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The Neutron Enigma
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SCIENTIFIC AMERICAN
Stone Age Brains
Toolmaking shaped how our minds think today
SPECIAL REPORT
FUTURE OF MEDICINE:
CANCER
IMMUNITY BOOSTERS
NEW VACCINES
GENE THERAPIES

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ON THE COVER

Making ever more sophisticated tools may have helped drive brain evolution beginning 2.6 million years ago. To better understand the relation between toolmaking and evolution, contemporary researchers use brain scanners, looking under the skull as people replicate the crafting of Paleolithic hand axes and other implements. **Illustration by Mark Ross.**

Photograph by Gregory Miller

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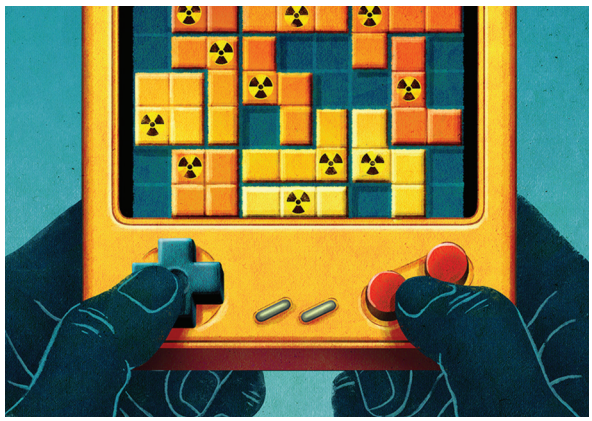

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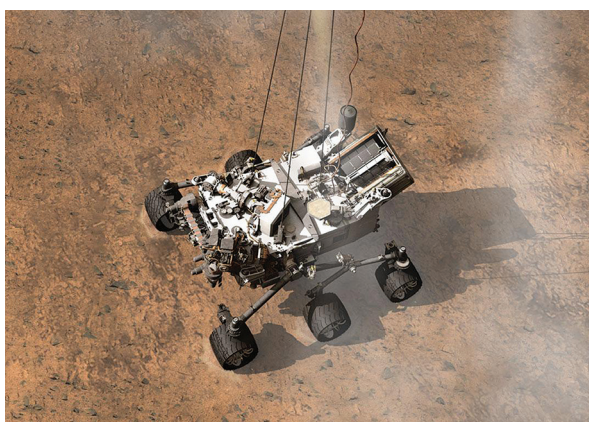

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ON THE WEB

Gravitational Waves Detected
Scientific American examines the huge impact that the Laser Interferometer Gravitational-Wave Observatory (LIGO) experiment is having on astronomy.
Go to www.ScientificAmerican.com/apr2016/ligo

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FROM THE EDITOR

Rocks in Our Heads

"We did get some funny looks when we first started wheeling carts of rocks into a state-of-the-art neuroimaging lab," writes Dietrich Stout in this issue's cover story, "Tales of a Stone Age Neuroscientist," starting on page 28. What were they doing? A bit of experimental archaeology designed to help scientists understand the evolution of our higher mental faculties.

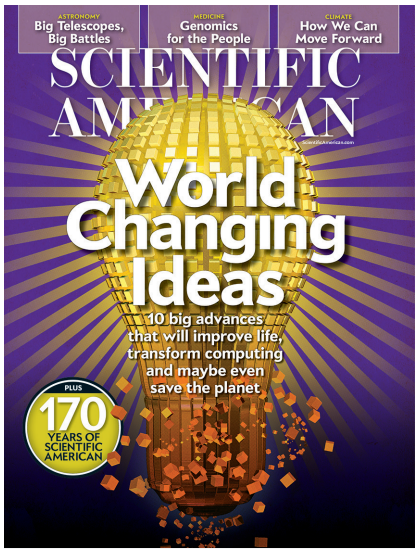
Among other experiments, volunteers chipped away at hunks of stone, shaping them into an ax or a knife. Afterward, neuroimaging recorded how the activity had changed the brain. Stout, who says it took some 300 hours to learn to chip stone properly himself, and others are finding insights into our ancient selves through scans of the brains of modern humans who have been making such stone implements. Put another way, while the ancients sculpted the world around them, their toolmaking helped to shape what's inside our skulls today. As it turns out, both manual and language skills may rely on some of the same brain structures. Stout and others have proposed that the neural circuits that got rewired in toolmaking were then co-opted to support early forms of communication, including gestures and maybe even vocalizations. Continuing experiments will help put those ideas to the test, giving new (positive) meaning to the idea of having "rocks in our heads."

Brains are often thought of as our mental "computers." Now, taking processing to a new level, synthetic biologists are developing ways to put living cells to work as biocomputers. A tiny bit of computing logic in a living cell could detect disease in patients or be used in numerous ways in agriculture or pharmaceutical manufacturing. Timothy K. Lu and Oliver Purcell describe various facets of "Machine Life," starting on page 58.

One of the pleasures of the human brain, as opposed to other thinking machines, is its ability to wonder. For me, at least, the fundamentals of how the universe might work never cease to inspire. Consider the puzzle of the neutron lifetime. Inside an atomic nucleus, a typical neutron endures for long periods. But outside of that, Geoffrey L. Greene and Peter Geltenbort write, it will decay "in 15 minutes, more or less." Two precision experiments can't agree on how long neutrons live. Is the cause measurement errors or some deeper mystery? Therein, beginning on page 36, lies "The Neutron Enigma." SA

Mariette DiChristina is editor in chief of *Scientific American*. Follow her on Twitter @mdichristina

Photograph by Gregory Miller (book); Illustration by Nick Higgins (DiChristina)



December 2015

PREDICTING BIPOLAR

Kevin A. Strauss's otherwise excellent article, "Genomics for the People," about the wonderful research and services being carried out for Amish and Mennonite families at the Clinic for Special Children in Strasburg, Pa., gives the impression that there is a genetic test that can "inform us about a child's risk for bipolar disorder 30 years hence." Unfortunately, no such test exists. Bipolar disorder is associated with numerous genes and nongenetic risk factors. No single gene is necessary or sufficient.

Genetic research is important to understanding the origins of many mental illnesses. But tests that can make useful predictions are not yet on the horizon.

Francis J. McMahon
Chief, Human Genetics Branch, National Institute of Mental Health
President, International Society of Psychiatric Genetics

STRAUSS REPLIES: McMahon, a leader in psychiatric genetics, makes a familiar claim about the multifactorial nature of mental illness and is correct to point out that no single genetic test can unequivocally predict a person's risk for bipolar disorder. Nevertheless, among the people we serve, a rare alteration in a gene called KCNH7 *does appear to confer a major risk for this seemingly complex disease. We screened a total of 394 Amish research subjects for the* KCNH7 *mutation; 84 of these individuals carried at least one copy of the gene variant, and the lifetime incidence of bipolar spectrum disorders among them was 49 percent (41 people were affected with the disease). For comparison, the aggregate lifetime prevalence of bipolar spectrum disorders worldwide is about 2.4 percent. Thus, this single genetic test can indicate a risk for bipolar illness that is 20-fold higher than that of the general population. This is useful clinical information and suggests that Amish people with the mutation should be monitored carefully and offered intervention as soon as symptoms arise.*

"Three very large telescopes are the least that will be needed to enable the astronomical research of coming decades."

AUGUSTUS OEMLER AND ALAN DRESSLER
CARNEGIE OBSERVATORIES

VERY LARGE TELESCOPES

We were very disappointed in "Telescope Wars," by Katie Worth. Contrary to the article's assertions, "bitter rivalries" from the past played a very small part in the history of the Thirty Meter Telescope (TMT) and Giant Magellan Telescope (GMT) projects. Why the Carnegie Institution for Science's repeated attempts to join the TMT project were rebuffed is a complicated story that only those at the California Institute of Technology and the University of California know completely, but it is clear that the internal dynamics of the partnership and the desire to control the technical development of the telescope played large roles. We at Carnegie eventually gave up when it became clear that we could never be more than a small, passive partner and when J. Roger Angel's development of the GMT concept provided a more attractive alternative.

Further, the article's claim that there are insufficient funds in the U.S. to support two such projects is faulty. Both the GMT and TMT are international collaborations, with about 80 percent of the TMT's funding coming from outside the U.S. and about 20 percent of the GMT's. In effect, U.S. resources are providing the funding for only one telescope. Three very large telescopes—the GMT, the TMT and the European Extremely Large Telescope—are the least that will be needed to enable the astronomical research of coming decades. There is no evidence, nor is it sensible to believe, that either the TMT or GMT would be much advanced if more money had been available; the technical challenges of very large telescopes are daunting, and these have set the pace.

Augustus Oemler
Alan Dressler
Carnegie Observatories

CARBON TAX

Thank you for advocating for a carbon tax in "The Price of Pollution" [Science Agenda]. We at Carbon Washington, a grassroots organization of students, community members and economists, agree that a carbon tax is an economically feasible way to reduce air pollution caused by CO_2-emitting fossil fuels.

Last December we submitted more than 360,000 signatures to Washington's secretary of state for our statewide, revenue-neutral carbon tax initiative, I-732, which would institute a tax of $25 per metric ton of CO_2 on fossil fuels in the state. If I-732 succeeds at the polls, we hope that it can serve as a model for other states to implement their own carbon tax systems.

Jen Monnier
Carbon Washington

One benefit of a national carbon tax the article fails to mention is improved health. As a carbon price reduces coal, oil and gas use, fewer Americans will get sick.

Gideon Forman
Toronto

CLIMATE CHANGE DENIAL

In "Consilience and Consensus" [Skeptic], Michael Shermer's arguments demonstrate *how* deniers of anthropogenic global warming (AGW) are wrong. But he doesn't give reasons for *why* they deny AGW.

If we look for patterns among skeptics, a characteristic comes to light: they are extremely religious and conservative. At a fundamental level, they cannot accept that human beings have the power to destroy God's work. Senator James Inhofe of Oklahoma, for example, said: "The arrogance of people to think that we, human beings, would be able to change what [God] is doing in the climate is, to me, outrageous."

JAIME VALDIVIESO
El Puerto de Santa María, Spain

SHERMER REPLIES: Senator Inhofe's antics on the Senate floor are embarrassing to most thoughtful Christians. Fortunately, he and other conservative Christians are being challenged by climate scientist Katharine Hayhoe, who also happens to be an evangelical Christian on a crusade to demonstrate to her fellow believers why being a Christian is not in conflict with accepting climate change.

In my opinion, however, the denial of climate change is driven more by economic ideology than religious belief, primarily the fear that if climate change is real and voters decide that we ought to do something about it, that something might include the curtailment of polluting industries.

ERRATA

"The Heat Vacuum," by Rachel Nuwer [World Changing Ideas], incorrectly refers to silicon dioxide atoms behaving like antennas. It should have referred to molecules of silicon dioxide. The article also says the material discussed radiates at wavelengths between eight and 13 nanometers; the correct measurement is eight to 13 microns.

"The Big Bang's Particle Glow," by Shannon Hall [Advances], states that there are 10 billion particles of matter in the universe for every one antimatter particle. The universe does have many more particles of matter than antimatter, but the exact ratio is unknown.

Quick Hits [Advances] indicates that Australia's new curriculum for elementary school students will replace history and geography with computer coding. History and geography will still be taught, though within a new single humanities and social sciences subject.

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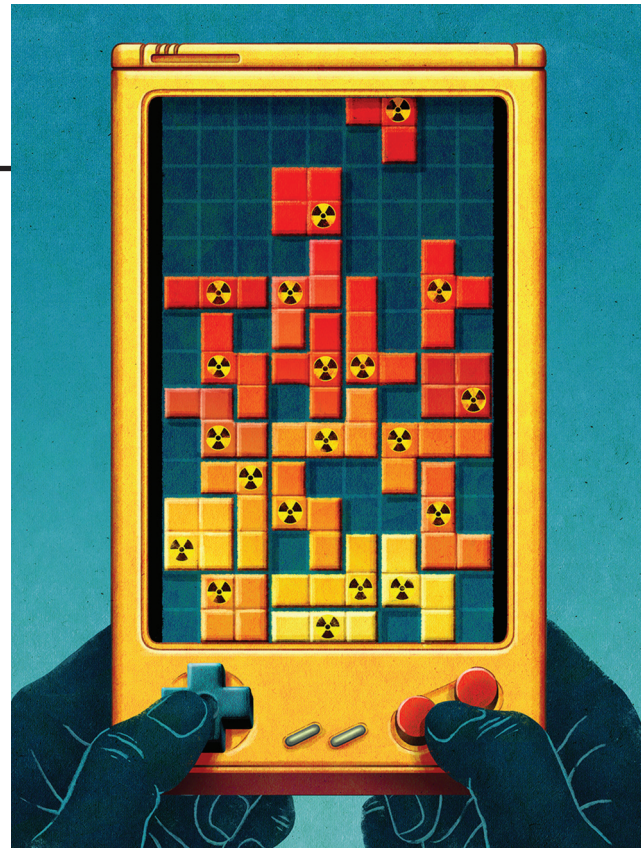
Stop Dithering on Nuclear Waste

Three decades after Chernobyl, the U.S. needs to tackle its own ominous nuclear safety problem

By the Editors



April marks the 30th anniversary of the world's worst nuclear power disaster, the explosion and fire at a reactor at the Chernobyl plant in Ukraine, in the former Soviet Union. It forced more than 300,000 people to flee and created a zone tens of kilometers wide where radiation levels remain hazardous to this day.

A severe reactor accident is unlikely in the U.S. and other countries with safer facilities. But we face another danger that is in many ways more threatening than a meltdown: the steady accumulation of radioactive waste. The U.S. has dithered over this clear and present danger for decades, irresponsibly kicking the can down the road into the indefinite future.

The spent fuel produced by nuclear power plants will emit harmful radiation for hundreds of thousands—even millions—of years. Some 70,000 metric tons of it are now stored at 70 sites scattered across 39 states. One in three Americans lives within roughly 80 kilometers of a storage site. The waste, hot from radioactive decay, is held in deep pools of water or in "dry casks" of concrete and steel that sit on reinforced pads. Accidents or terrorist attacks could drain the pools or crack the casks, with the risk that the exposed waste could catch fire, spreading radioactive soot across the surrounding countryside and into food chains in a Chernobyl-like catastrophe. As the years go by and waste is packed into overcrowded pools and pads, that risk will only grow.

An acceptable solution to this unacceptable state of affairs has been in the works for more than 30 years. The Nuclear Waste Policy Act of 1982 established a framework for the permanent disposal of the nation's nuclear waste, leading to the 1987 selection of Yucca Mountain, a barren peak in the high desert of Nevada, as the site of a deep geologic repository that would be built and operated by the Department of Energy.

At Yucca, spent fuel housed in steel canisters would be sealed within tunnels above the water table, in a manner meant to minimize corrosion and possible leakage of radioactive material, even over geologically long periods. But because of strident political opposition from Nevadans, as well as vexing scientific uncertainties over the site's geologic suitability, President Barack Obama halted work on the repository in 2010. Today Yucca Mountain's fate remains in limbo. The danger aside, the lack of such a repository also stacks the deck against nuclear power as a viable, low-carbon tool for counteracting climate change.

In the aftermath of Yucca's mothballing, the DOE has pursued a diverse strategy of nuclear waste management that includes tentative plans for consolidated interim storage facilities, tests of deep boreholes as another possible long-term storage technique, and the development of "consent-based" siting protocols to gain support from municipal and state governments. But these measures will take us only so far. Experts agree that a geologic repository remains the only viable long-term solution for disposing of the majority of commercial nuclear waste.

Creating the repository is both scientifically and politically possible. Last year Finland showed this when it approved construction of the Onkalo facility, which is expected to become the first geologic repository for spent fuel when it begins operations in the 2020s. And even in the U.S., the Waste Isolation Pilot Plant (WIPP) in New Mexico currently stores waste from the production of nuclear weapons. (WIPP is neither designed nor approved to store spent fuel.)

Soon a new president will occupy the White House, and there will be a renewed opportunity to address the urgent issue of the U.S.'s nuclear waste. The decision to close Yucca Mountain must be revisited, and the selection and characterization of alternative sites should be aggressively accelerated. In the interim, more spent fuel should be moved from cooling pools to dry casks, which offer better protection against hazards.

Ultimately, if consent-based siting efforts fail, in favor of the common good the federal government must exercise its power of eminent domain to overcome local opposition, creating a deep geologic repository for nuclear waste. Regardless of whether the next president is for or against nuclear power, he or she must act decisively to avoid poisoning our shared future. SA

SCIENTIFIC AMERICAN ONLINE
COMMENT ON THIS ARTICLE AT
SCIENTIFICAMERICAN.COM/APR2016

Illustration by Julia Yellow

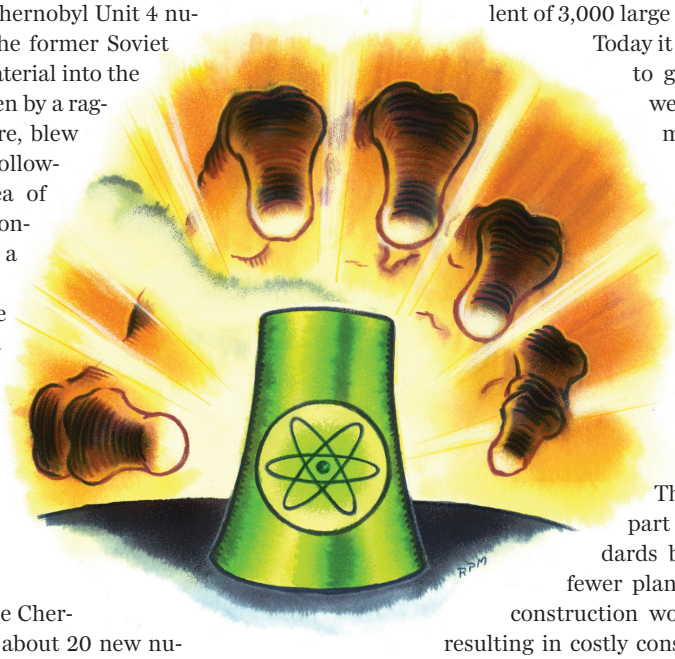
Frank von Hippel is a senior research physicist and professor of public and international affairs emeritus in the Program on Science and Global Security at Princeton University.

Chernobyl Didn't Kill Nuclear Power

The accident was just one factor that makes it a hard sell to fight climate change

By Frank von Hippel

Thirty years ago, at 1:24 A.M. on April 26, 1986, explosions blew the lid and roof off the Chernobyl Unit 4 nuclear reactor in Ukraine, in the former Soviet Union, blasting radioactive material into the atmosphere. The outflow, driven by a raging fire within the reactor core, blew in all directions during the following week. Ultimately an area of 3,110 square kilometers was contaminated with cesium 137, to a level requiring evacuation.



Superficially, it is reasonable to leap to the conclusion that fear generated by the Chernobyl disaster turned the public against nuclear power—so strongly that even now, three decades later, there is serious doubt that it will ever be a major alternative to climate-threatening fossil fuels. In the 15 years before the Chernobyl accident, an average of about 20 new nuclear power reactors came online each year. Five years after the accident, the average had dropped to four a year.

But the full story is more complex. The effects of Chernobyl on people, though significant, were not devastating. Beyond the evacuation area, it is estimated that the radiation will cause tens of thousands cases of cancer across Europe over 80 years. That may sound like a large number, but it is a mostly undetectable addition to the background cancer rate. One exception is thyroid cancer, caused by the ingestion of radioactive iodides: there have been visible epidemics—only 1 to 2 percent fatal, fortunately—in the most affected regions of Belarus, Russia and Ukraine.

Despite the projected cancer deaths from Chernobyl and the 2011 Fukushima Daiichi disaster in Japan, however, nuclear power still appears safer than coal, measured in terms of average deaths per unit of electric energy generated. According to a 2010 study by the National Research Council, if the U.S.'s then 104 nuclear reactors had been replaced in 2005 with coal plants, the increased air pollution would have caused thousands of additional premature deaths annually.

People also tend to worry more, however, about the long-term impact of radiation than they do about the effects of air pollution. A survey of the psychological well-being of Ukraine's population 20 years after Chernobyl found that an extra radiation dose equivalent to one year's natural background exposure was correlated with reduced life satisfaction, an increase in diagnosed mental disorders and a reduction in subjective life expectancy.

Such worries contributed to the drop in new plant construction post-Chernobyl, but there were other reasons. One was that the growth of electric power consumption in developed countries slowed dramatically at around the same time because the price of electricity stopped falling. In 1974 the U.S. Atomic Energy Commission was projecting that the U.S. would require the equivalent of 3,000 large nuclear power reactors by 2016. Today it would take just 500 such plants to generate as much electricity as we consume on average—although more capacity would be required for times of peak consumption.

Another factor is that, contrary to the claims of boosters in the 1950s that nuclear power would be "too cheap to meter," it is quite expensive. Fuel costs are low, but construction costs are huge, especially in North America and Europe—$6 billion to $12 billion per reactor. This expense has been driven in part by more stringent safety standards but also by the fact that, with fewer plants being built, there are fewer construction workers qualified to build them, resulting in costly construction delays for corrections of mistakes. The future of nuclear power is now largely in the hands of China. About half of the nuclear power reactors under construction starting in 2008 are located there, and China's nuclear industry is beginning to propose projects in other countries. China's rate of construction is still far below that of the U.S. and Western Europe in the 1970s, however, and the world is consuming electric power at three times the rate it did then. The International Energy Agency projects that the nuclear share of China's electricity generation will grow to only 10 percent by 2040.

On the scale needed to shift human energy use away from fossil fuels, therefore, nuclear power has become a helpful but relatively marginal player. Chernobyl damaged its prospects, but it was not the only reason for the technology's decline. SA

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Illustration by Ross MacDonald

ADVANCES

The lions in Serengeti National Park hold claim to being the only large population in East Africa not in decline.

INSIDE

CONSERVATION

Lions on the Ledge

The big cats are making a surprising comeback—but only when they are kept behind fences. What will it take to produce more satisfying gains?

In the summer of 2015 a single dead lion, Cecil, dominated the news. Trophy hunting is not without its complications, but *Panthera leo* faces even larger problems than wealthy hunters with big guns. Classified as threatened, lions suffer from habitat loss, depletion of prey, retaliatory killing for real or perceived losses of human life and livestock, poaching for traditional medicine, and more. In Africa these big cats have been relegated to just 17 percent of their historical range, and just one population survives elsewhere, isolated in India. New research reveals that although the state of African lions seems dire, in some places the cats are actually thriving. But these success stories aren't as straightforward as they first appear, and the future well-being of lions in Africa won't come cheap.

Although the king of the jungle is fairly well studied, most research efforts have focused on individual populations rather than the entire species, which is down to perhaps as few as 20,000 individuals. By combining data from them, researchers can now take continent-wide views of the

state of Africa's most iconic predator. In the latest study of this kind, a group of researchers led by University of Oxford zoologist Hans Bauer compiled data from surveys of 47 lion populations conducted over the past 20 years. They found that each of the nine lion populations in West Africa, save for one, is in decline (and two populations in that area might already be locally extinct). Lions in East Africa also are faring poorly; the Serengeti population is the only large group there for which the predictions skew positively. According to the conservative analysis, there is a 67 percent chance that the West African lion population will be halved 20 years from now, whereas the odds for the East African cats are around 37 percent.

The analysis also revealed a glimmer of hope: most of the lions in southern Africa are thriving. On this part of the continent, "lion populations are very likely to persist," says University of Minnesota lion expert Craig Packer, who oversaw the study, which was recently published in the *Proceedings of the National Academy of Sciences USA*. Why? Either they live in deserts so remote and inhospitable that humans pose little threat, or they live in fenced-in parks and reserves.

Even small fenced reserves have conservation value, according to Peter A. Lindsey, a researcher at the conservation organization Panthera who was not involved in the study. "Any land we can get under protection can contribute to conservation. So the more, the better," he says. Fences allow lions and other wildlife to survive on fragments of land on which it would otherwise be impossible to conserve large mammals because they keep big animals from coming into conflict with humans, livestock and agriculture. In many places the only reason conservancies can work to restore populations at all is because local communities have been reassured that these barriers will keep them safe.

Not all biologists see fences as the saving grace of lions, however. Enclosed lions make only "limited contributions to ecosystem functionality," Bauer and his colleagues wrote in their study. Does fencing turn a landscape into little more than a glorified zoo, lions into a pricey tourist attraction?

If a fenced area is large—South Africa's mostly fenced Kruger National Park is nearly the size of New Jersey—then the lions still can perform their roles as apex predators and regulate the ecosystem by controlling populations of antelope, buffalo and other ungulates, which in turn help to maintain plant communities. Despite the artificially imposed boundaries, "nobody doubts that Kruger is a real ecosystem, with real ecosystem processes in it," Packer says.

If land managers in Africa were as well funded as Yellowstone National Park, they could afford to manage the average unfenced lion population at around two-thirds its potential size, a step up from the current status quo.

But most fenced areas are quite a bit smaller. "If you contain wildlife in small, fenced, protected areas, you have to manage it quite intensively because the population dynamics seem to go a bit crazy," Lindsey says. "And the reasons for this are not particularly well understood." Intensive management can include implanting females with hormonal contraceptives to prevent overpopulation, as well as capturing and moving individuals to other reserves to bolster genetic diversity. If new genes are not regularly introduced into a small group of lions, they run the risk of inbreeding, which can cause a population to collapse.

This involvement helps, but it is not a cure-all. "The lion community as a whole needs to realistically come to grips with our priorities and the priorities of [local] communities," says Institute of Zoology researcher Andrew Jacobson. A fence would be impractical, for example, in places where it would impede wildlife migrations, such as the wildebeest that chase the rains across the Serengeti every year.

No matter which side of the fence they fall on, most lion researchers agree that the future of lions in Africa hinges more on dollars than fences. Many African parks and reserves struggle because they are chronically underfunded. According to a 2013 analysis conducted by Packer, it is cheaper to manage lions in fenced reserves at around $500 per square kilometer (not counting the high cost of installing the fence in the first place) than in unfenced areas, where $2,000 is only sufficient for managing a population at half its potential density. But an analysis by Montana State University researcher Scott Creel found that, dollar for dollar, spending on unfenced areas helps more individual lions.

Indeed, if land managers in Africa were as well funded as Yellowstone National Park, at around $4,100 per square kilometer, they could afford to manage the average unfenced lion population at around two-thirds its potential size, a step up from the current status quo. Despite the utility of ecotourism and trophy hunting for lion conservation in general, only a small proportion of that revenue typically becomes available to wildlife managers.

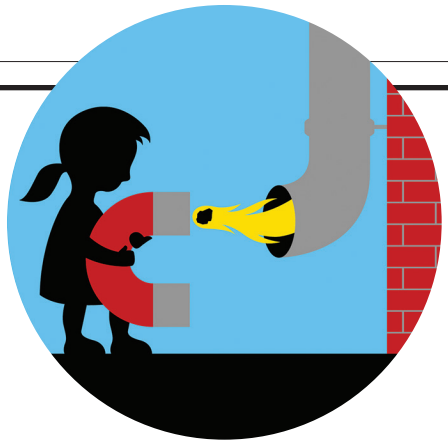
In places where ecology renders fences impractical, funding is critical for providing an economic incentive for locals to tolerate the costs of coexisting with large carnivores, such as losing livestock to hungry lions or keeping their flocks from grazing on protected land. Indeed, if lions' wild prey is edged out by the grazing livestock of a swelling African population, they will have no choice but to develop a taste for beef. That, in turn, could provoke more retaliatory killings, and lions will feel the squeeze from each side as they suffer both from direct conflict with humans and from having less to eat. Some ecosystems will benefit from fences, whereas other populations will require conflict-mitigation projects, but all such efforts will require a lot more money.

So the latest insights do offer a path forward: lions can still have a home in Africa well into the future so long as the international community is willing to finance it. "If the level of funding for Africa's protected areas can be increased," Lindsey says, "there's no reason why the existing protected areas couldn't carry a lot more lions."

—Jason G. Goldman

PRECEDING PAGES: MICHAEL NICHOLS *Getty Images*

COMMENT AT ScientificAmerican.com/apr2016



CITIZEN SCIENCE

April Showers Bring May Meteorites

How to find small pieces of outer space at home

Massive meteorites are mercifully rare, but their miniature counterparts constantly bombard Earth. NASA estimates that approximately 100 tons of space dust, gravel and rock of various diameters hit our planet every day. "If you get down to the size of a marble, there's about one of those to be picked up about every square kilometer across Earth's surface," says civilian astronaut and meteorite hunter Richard Garriott. "Once you get down to the size of a grain of rice, they're incredibly common."

In fact, your roof may harbor a handful of micrometeorites. Most land in the ocean, but some fall over cities and suburbs and collect in the nooks and crannies of roofs. When it rains, that debris often gets swept into gutters.

To locate the nickel- and iron-laden rocks, Garriott runs a strong magnet over the cracks between garden tiles where a gutter downspout terminates. Not everything the magnet attracts will come from space. Construction residue, such as shavings from a nail or some natural stones used for patios, also may latch onto a magnet. But separating the wheat from the chaff is relatively easy: micrometeorites are spherical and sport "crusting," a telltale coating of glass created under fusion. The best way to confirm the feature is with a microscope.

Garriott is hardly the only enthusiast scouring his porch for celestial treasures: amateurs have submitted more than 3,000 photographs of candidate space rocks to Project Stardust, an independent investigation into micrometeorites that encourages citizen scientists to share their finds. —*Jennifer Hackett*

Illustrations by Thomas Fuchs

NUTRITION

A Twist on the Mushroom Burger

Restaurants and schools trade in all-beef dishes for a healthier fungal hybrid

One of the biggest scientific experiments in American schools this year has unfolded not in a petri dish but in a patty. Instead of all-beef burgers, students in more than 300 school districts across the country have been eating "The Blend," a meat-mushroom amalgam.

This mash-up has its roots in a "healthy flavors" initiative from the Culinary Institute of America, which teamed up with the Mushroom Council in 2011 to explore how the umbrella-shaped fungi could trim the dietary sins of common beef dishes. The groups then partnered with Jean-Xavier Guinard, a sensory scientist at the University of California, Davis, who runs a flavor laboratory specializing in testing and characterizing food tastes. In 2014 The Blend was born.

Why use mushrooms as a stand-in for beef? They contain a chemical cocktail that yields a meaty taste called umami, Japanese for "delicious." But in contrast to beef, mushrooms boast fewer calories, less sodium and no saturated fat. Those nutritional benefits have persuaded school districts, which must meet national health standards, to try the mixture. For instance, last fall school food provider Sodexo replaced its conventional burgers with versions containing 30 percent mushroom (the percentage counts as a full serving of vegetables). If Sodexo serves the same number of burgers this school year as it typically does, it projects students overall will consume a total of approximately 16 million grams less saturated fat and 300 million milligrams less sodium.

Mushrooms also provide a green alternative to red meat. Their vendors have yet to quantify environmental impacts, but Kirk Broders, an assistant professor of bioagriculture at Colorado State University, sees promise. "It would be much more sustainable than livestock production," he notes. Mushrooms require relatively few resources to flourish: commercially grown varieties thrive on manure and carbon-rich agricultural by-products such as corn husks. They also do not require the space and antibiotics that livestock do. Plus they reach maturity much faster.

Despite reports of successful replacements, The Blend does not work in all dishes. In one recent blind taste test, 147 participants sampled carne asada and taco-filling mixes featuring a range of beef and mushroom percentages. Although more than half of them preferred mushroom-mixed taco blends to pure-beef ones, many subjects gave low marks to a mushroom-laden carne asada for texture and appearance. "When you're eating carne asada, you're expecting strips of beef," Guinard says. "In the taco blend, where the stuff is ground small, you really don't see it."

If the burgers perform well in schools, however, they may soon debut in office cafeterias, too. National restaurant chains, including Pizza Hut and Seasons 52, have also quietly slipped blended entrées onto their menus in a quest for healthier offerings. All that means The Blend could be the burger of the future. That is, until lab-grown patties come along.

—Natalie Jacewicz

SPACE

Passengers Announced for NASA's Biggest Rocket

Thirteen small satellites will hitch a ride before humans do

In 2018 the Space Launch System (SLS), the most powerful rocket ever built, will blast off into deep space. The event will serve as an astronaut-readiness test, but 13 shoe-box-sized satellites—called CubeSats—will take advantage of the "free" ride off Earth. NASA recently announced a handful of these mini missions, and their goals are as different from one another as the moon is from an asteroid. A sampling includes:

COURTESY OF NASA MARSHALL SPACE FLIGHT CENTER (*artist's conception*)

NEAR-EARTH ASTEROID SCOUT

The NEA Scout satellite will collect data about the spin, topography and surface compositions of asteroid 1991 VG, a near-earth object that could become a landing site for future spacecraft. ***Project of NASA Marshall Space Flight Center and NASA Jet Propulsion Laboratory***

BIOSENTINEL

This CubeSat is set to carry the first living organisms beyond low-Earth orbit since 1972: yeast. During the 18-month mission, a multitude of sensors will monitor the type and intensity of radiation the yeast encounter, as well as how they fare. Radiation exposure is a major concern for upcoming crewed missions headed for more distant destinations, such as Mars. ***Project of NASA Ames Research Center***

CUSP (CUBESAT TO STUDY SOLAR PARTICLES)

This weather station comes packed with a magnetometer, ion spectrograph and miniaturized proton telescope. It will monitor space events in real time, including incoming radiation and solar wind, in an effort to understand how geomagnetic storms form and affect Earth. ***Project of NASA Goddard Space Flight Center and Southwest Research Institute***

LUNAR ICECUBE

As it orbits the moon, Lunar IceCube will perform the most comprehensive scan of Earth's satellite for water to date. Previous probes have found traces of the molecule, but this one is optimized to detect water in all its forms. Accessible resources in space are considered essential for longer crewed missions. ***Project of Morehead State University***

CUBE QUEST CHALLENGE TOURNAMENT WINNERS

In 2017 three missions will be chosen from entries submitted by Americans unaffiliated with NASA or other government agencies. Prizes will be awarded to the teams that enter lunar orbit, travel the farthest into space or maintain the longest communication with Earth.

—Jennifer Hackett

Q&A

Forecaster for the Top of the World

SCIENTIFIC AMERICAN talks with Michael Fagin, a meteorologist who issues weather predictions that could mean the difference between life and death

Mount Everest presents endless challenges to the adventurer who dares to seek its summit: treacherous overpasses, tumbling house-sized blocks of ice and hypoxic conditions, to name a few. Weather, too, poses an acute danger on the world's highest peak. In 1996, for example, a now infamous blizzard overtook the mountain, costing eight climbers their lives. Although heart attacks, falls and avalanches cannot be anticipated, weather—at least to some extent—can. Michael Fagin, a Seattle-based meteorologist, is the go-to man for prudent climbers. Every spring major expeditions, as well as intrepid individuals, hire him to provide daily forecasts for Everest and other Himalayan peaks. Edited excerpts follow. —*Rachel Nuwer*

What weather peculiarities affect Mount Everest?

It's common to have winds at 100 mph, but in May—the most popular time to climb, just before the monsoon starts—there are usually several days with winds at reasonable levels (under 20 mph). Another abnormal atmospheric condition that you have to

COURTESY OF ALAN L. BAUER, WWW.ALANBAUER.COM (*fagin*); JONATHAN GRIFFITH *Getty Images (Everest)*

A record number of people applied for permits to climb Mount Everest in 2015, but for the first time in 41 years, no one reached the summit.

The mountain was effectively shut down after a devastating earthquake hit Nepal in April and triggered avalanches.

be tuned into is cyclones that form in the Bay of Bengal. Although Everest is about 1,500 miles to the north and not at sea level, these storms can greatly impact the mountain, bringing heavy precipitation.

How is forecasting weather on Everest different than doing so for, say, Seattle?
The biggest difference is a lack of real-time weather observation. After I make a forecast, I cannot verify how accurate it was, because there are no weather stations on Everest. So I depend on climbers to send observations via e-mail. And while weather models in a place like Seattle provide excellent detail on a local level, for Everest the models are not on a regional scale but rather a global one—for the entire continent of Asia or the Himalayan range.

What's a typical day of work like for you during climbing season?
At 5 A.M. I look over feedback from climbers on the prior day's forecast to see which of the at least six models I use had the best handle on actual conditions—for example, the model issued by the Navy Operational Global Atmospheric Prediction System or the European Center for Medium-Range Weather Forecasts. I also look at dispatches from nonclients posted on Twitter, Facebook, Instagram and blogs. If one of the models has provided better accuracy over recent days, I'll assign a higher-weighted average for it. I'm finished by 9 A.M., but climbers in Nepal are more than half a day ahead and want updates first thing in the morning, so I take another look at 7 P.M. my time and make adjustments if needed.

How do you convey uncertainty?
I always give a "confidence rating" for my forecasts, which is critical because sometimes I'm highly confident but other times not.

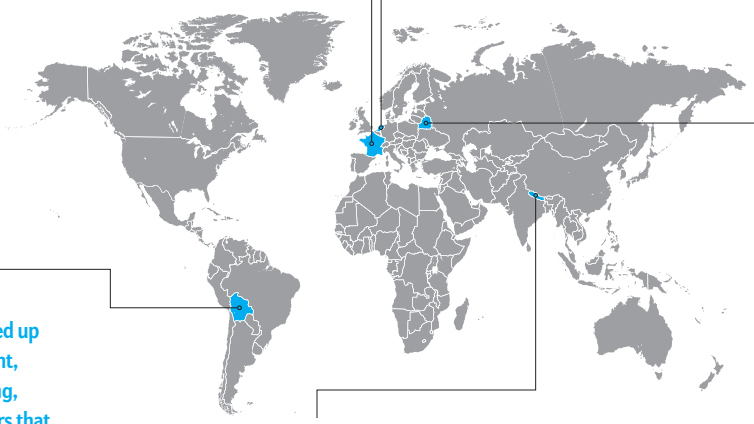
Have mountaineers ever gotten angry at you because of a forecast?
One year summit winds on a Tuesday were 100 mph, and I told the expedition leader that the winds would still be strong Wednesday and Thursday. He took the entire group back down to a lower camp. Someone in the group became very angry, however, when the winds on Thursday proved not very strong, but at that point his summit bid was nixed.

IN THE NEWS

Quick Hits

FRANCE
The French government announced it will "pave" 1,000 kilometers of public roads with solar panels. Installed over the next five years, the high-tech streets could supply electricity to about 8 percent of the country's population.

NETHERLANDS
The Dutch national police partnered with a raptor-training company to add eagles to their antidrone arsenal.



WORLD
4/4/16 is a Square Root Day. Only nine days in each century qualify, and the next one occurs in 11 years.

BELARUS
The country now owns its first satellite, Belintersat-1. It joins Laos, Venezuela and Nigeria in operating telecommunications satellites built—and launched—in China.

BOLIVIA
Lake Poopó, formerly the country's second-largest lake, has nearly dried up because of a combination of drought, water use for agriculture and mining, and the shrinking of Andean glaciers that serve as its source. The remains of the lake have been declared a disaster site.

NEPAL
Few people will ever summit Mount Everest, but virtual-reality studio Sólfar aims to bring more of us closer to the experience. This spring the company will release software for VR headsets that offers a danger-free trek up the earth's highest peak.

For more details, visit
www.ScientificAmerican.com/apr2016/advances

ANIMAL BEHAVIOR

Orphaned Bugs Make Bum Parents

Earwigs hand trauma down to their offspring

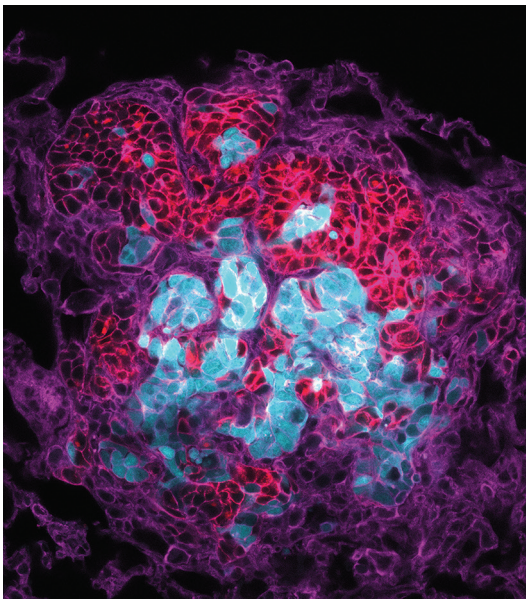
TIM SHEPHERD *Getty Images*

Some scars run deeper than others, and the early loss of a parent can be one of the most life altering. Many mammalian species, including humans, are known to pass this trauma to the next generation. Now biologists have shown that orphaned insects, too, interact differently with their own progeny. As reported in the *Proceedings of the Royal Society B,* larval earwigs left to fend for themselves grow up to become less than caring parents.

Unlike most vertebrate species, earwig young can survive on their own if necessary. So Joël Meunier, an evolutionary biologist then at Johannes Gutenberg University Mainz in Germany, and his colleagues wondered how the absence of a mother ran through this pincered arthropod's family. In their experiment, 40 earwig mothers raised a total of 1,600 nymphs; another 1,600 nymphs were left to fend for themselves in isolation. The researchers found that nurtured female nymphs matured into devoted moms—assiduously cleaning eggs and feeding and defending nymphs. In contrast, female earwigs raised without mothers did not excel as caregivers. They fed offspring less frequently and were not as effective at protecting them from predators.

The trauma most likely has a genetic component. The biologists also observed that even when the young of orphaned mothers were raised by foster parents, those babies still received less adequate care than the controls did. Such results suggest that an aspect of poor care is inherited.

Studies of insect parenting can provide insight into the origins of family dynamics and social behavior, says Meunier, who is now at the University of Tours in France. "There are not many arthropod species with parental care," he notes. "But those that do can help show us how family life evolved and why." —*Rachel Nuwer*



BIOLOGY

Cancerous Co-conspirators

Tumor cells that travel in a group are responsible for spreading disease

Metastasis is behind the vast majority of cancer deaths: when cancer cells break away from a tumor and lodge in new places, the disease becomes harder to treat. A new study shows that, contrary to expectations, most metastatic tumors are seeded not by single cells from the primary tumor but by clusters of diverse cancer cells that leave in a group and travel through the bloodstream together. The cells in these circulating clusters communicate with one another and produce specific proteins that could be used as drug targets or biomarkers for risk of metastasis.

To determine how metastases form, cancer cell biologist Andrew Ewald and his team at Johns Hopkins University created tumors in mice by injecting a mixture of multicolored cancer cells into the rodents' mammary glands. If tumors originated elsewhere from single cells, then they would show up under the microscope as one uniform color. If instead tumors were seeded by clusters of cells, then they would grow into rainbow-colored balls. The team found that about 95 percent of the cancers that formed were in fact multicolored and therefore derived from multiple cells (*lung metastasis, at left*).

In a second experiment, the researchers examined hundreds of cancerous cells grown together in a petri dish but placed so that they were not touching. Almost all of them died. In contrast, cells in another dish that were aggregated into clusters subsequently formed more colonies—even though there were fewer "seeds" to begin with. "Controlling for cell number, there is more than a 100-fold increase in efficiency of metastasis formation in the aggregated cells," Ewald says. The findings were published in February in the *Proceedings of the National Academy of Sciences USA*.

It is not yet entirely clear why the aggregated cells survive and metastasize more effectively, but it is likely that cooperation among tumor cells within clusters—for example, exchanging signaling molecules—protects against cell death in the bloodstream or at distant sites, explains Joan Brugge, a cancer cell biologist at Harvard Medical School who was not involved in the study.

> "We could potentially use this [insight] to develop targeted ways to attack all the metastatic cells."

As for potential benefits to patients, Ewald's team also found that the traveling clusters share molecular features and nearly all make the protein keratin 14. "We could potentially use this [insight] to develop targeted ways to attack all the metastatic cells," Ewald says. The idea would be to wipe out those cells wherever they are in the body, whether or not they are proliferating—a different approach from most standard therapies, which focus on attacking rapidly proliferating cells but not the circulating, invasive ones that initiate secondary cancers. —*Viviane Callier*

COURTESY OF BREANNA MOORE *Cheung Laboratory, Fred Hutchinson Cancer Research Center*

COMMENT AT ScientificAmerican.com/apr2016

ARCHAEOLOGY

Silk Road Heads for the Hills

Archaeologists uncover evidence for a previously unknown branch of the ancient trade system

Famous for facilitating an incredible exchange of culture and goods between the East and the West, the ancient Silk Road is thought to have meandered across long horizontal distances in mountain foothills and the lowlands of the Gobi Desert. But new archaeological evidence hidden in a lofty tomb reveals that it also ventured into the high altitudes of Tibet—a previously unknown arm of the trade route.

Discovered in 2005 by monks, the 1,800-year-old tomb sits 4.3 kilometers above sea level in the Ngari district of Tibet. When excavations began in 2012, the research team examining the site was surprised to find a large number of quintessential Chinese goods inside. The haul lends itself to the idea that merchants were traveling from China to Tibet along a branch of the Silk Road that had been lost to history.

"The findings are astonishing," says Houyuan Lu, an archaeobotanist at the Chinese Academy of Sciences' Institute of Geology and Geophysics in Beijing. Among other artifacts, archaeologists unearthed exquisite pieces of silk with woven Chinese characters *wang hou* (meaning "king" and "princes"), a mask made of pure gold, and ceramic and bronze vessels.

They also were taken aback by what looked like tea buds. The earliest documentation of tea in Tibet dates to the seventh century A.D., but these buds would be 400 to 500 years older. To confirm the identification, Lu and his colleagues analyzed the chemical components of the samples and detected ample amounts of caffeine and theanine, a type of amino acid abundant in tea. Moreover, the chemical fingerprints of the tea residues were similar to those of tea found in the tomb of a Chinese emperor of the Han Dynasty dated to 2,100 years ago, and both could be traced to tea varieties grown in Yunnan in southern China. "This strongly suggests that the tea [found in the Tibetan tomb] came from China," Lu says. The findings were recently published in *Scientific Reports.*

Such early contacts between Tibet and China "point to a high-altitude component of the Silk Road in Tibet that has been largely neglected," says Martin Jones, an archaeobotanist at the University of Cambridge. The evidence contributes to the emerging picture that the Silk Road—which the Ottoman Empire closed off in the 15th century—was a highly three-dimensional network that not only traversed vast linear distances but also scaled tall mountains.

Other studies, too, have documented signs of trade along mountain trails in Asia from around 3000 B.C.—routes now known as the Inner Asia Mountain Corridors. "This suggests that mountains are not barriers," says Rowan Flad, an archaeologist at Harvard University. "They can be effective conduits for the exchange of cultures, ideas and technologies." —*Jane Qiu*

SOURCE: "EARLIEST TEA AS EVIDENCE FOR ONE BRANCH OF THE SILK ROAD ACROSS THE TIBETAN PLATEAU." BY HOUYUAN LU ET AL., IN *SCIENTIFIC REPORTS*, VOL. 6, ARTICLE NO. 18955; JANUARY 7, 2016

Map by Mapping Specialists

Jeneen Interlandi is a New York City–based freelance journalist who covers health and the environment.

The Paradox of Precision Medicine

Early attempts to tailor disease treatment to individuals based on their DNA have met with equivocal success, raising concerns about a push to scale up such efforts

By Jeneen Interlandi

Precision medicine sounds like an inarguably good thing. It begins with the observation that individuals vary in their genetic makeup and that their diseases and responses to medications differ as a result. It then aims to find the right drug, for the right patient, at the right time, every time. The notion certainly has its supporters among medical experts. But for every one of them, there is another who thinks that efforts to achieve precision medicine are a waste of time and money. With a multimillion-dollar government-funded precision medicine initiative currently under way, debate is intensifying over whether this approach to treating disease can truly deliver on its promise to revolutionize health care.

Ask scientists who favor precision medicine for an example of what it might accomplish, and they are likely to tell you about ivacaftor, a new drug that has eased symptoms in a small and very specific subset of patients with cystic fibrosis. The disease stems from any of several defects in the protein that regulates the passage of salt molecules into and out of cells. One such defect prevents that protein from reaching the cell surface so that it can usher salt molecules back and forth. Ivacaftor corrects for this defect, which is caused by a handful of different genetic mutations and is responsible for roughly 5 percent of all cystic fibrosis cases. Genetic testing can reveal which individuals are eligible for this treatment.

The U.S. Food and Drug Administration fast-tracked development of ivacaftor a few years ago, and the drug been hailed ever since as the very essence of what of precision medicine is all about. Indeed, when President Barack Obama announced the launch of the government-funded precision medicine initiative in January 2015, he, too, sang ivacaftor's praises: "In some patients with cystic fibrosis, this approach has reversed a disease once thought unstoppable." Later the president declared that precision medicine "gives us one of the greatest opportunities for new medical breakthroughs that we have ever seen."

But ask opponents for an example of why precision medicine is fatally flawed, and they, too, are likely to tell you about ivacaftor. The drug took decades to develop, costs $300,000 a year per patient, and is useless in the 95 percent of patients whose mutations are different from the ones that ivacaftor acts on.

Moreover, a recent study in the *New England Journal of Medicine* found that the extent to which ivacaftor helped its target patients was roughly equal to that of three far-lower-tech, universally applicable treatments: high-dose ibuprofen, aerosolized saline and the antibiotic azithromycin. "These latter innovations are part of many small-step improvements in [cystic fibrosis] management that have increased survival rates dramatically in the past two decades," says Nigel Paneth, a pediatrician and epidemiologist at Michigan State University. "They cost a fraction of what the [high-tech] drugs cost, and they work for every patient."

The same paradox applies to nearly every example of precision medicine you can find: clinicians viewed the use of a patient's genotype to determine the right dose of the anticlotting medication warfarin as a godsend until some studies suggested that the approach did not work any better than dosing through old-fashioned clinical measures such as age, weight and gender. And the drug Gleevec was hailed as an emblem of targeted cancer therapy when it shrank tumors in a subset of leukemia patients with a very specific mutation in their tumors. But then a lot of those tumors developed new mutations that made them resistant to the drug, and when they did, the cancer returned. Gleevec bought patients time—a few months

Illustration by Lorenzo Gritti

here, a year there—but it did not change the final outcome.

The debate over the merits of precision medicine has its roots in the Human Genome Project, the 13-year, $3-billion (in 1991 dollars) effort to sequence and map the full complement of human genes. Building on that work, scientists devised a shortcut for linking particular gene variants to specific diseases with as little sequencing as possible. That shortcut, known as GWAS, for genome-wide association studies, involved examining selected sites across the genome to see which ones differed consistently between individuals who suffered from a certain medical condition and individuals who did not. Hoping for a bonanza of new drug targets, pharmaceutical companies invested heavily in GWAS. But the approach proved poor at exposing the genetic roots of disease. Study after study turned up many clusters of gene variants, any one of which could predispose someone to a condition. In most cases, these variants nudged risk up or down only by a tiny sliver, if at all. The results cast a pall on the notion of studying genetic variation to develop targeted therapies on a large scale.

Proponents of precision medicine argue that the problem is not the notion of exploring genetic differences per se but the extremely limited scope of GWAS. Instead of looking for a few types of common gene variants that correlate with disease, they say, researchers need to examine the entire genome—all six billion nucleotides, the building blocks of DNA. And they need to superimpose those data on top of several other layers of information about everything from family history to the microbes that inhabit the body (the microbiome) and the chemical modifications to DNA that affect how active individual genes are (the epigenome). If they compared all the data, among as many individuals as possible, they would finally be able to pinpoint which constellation of forces drive which diseases, how best to identify those forces and how to devise treatments that target them.

The precision medicine initiative that President Obama announced last year aims to do exactly that. Its centerpiece is a million-person cohort, from whom data of every conceivable kind—including genome, microbiome, epigenome—will be collected and stored in one colossal database, where scientists can access it for an endless array of studies and analyses.

To understand how all these data are supposed to help scientists conquer humanity's diseases, consider the example of warfarin. Knowing how fast or how thoroughly a person is apt to metabolize the drug should have made it easier to determine the best dose for that individual and should therefore have led to better outcomes. So why didn't it? Might diet or other factors play a role? Scientists do not know, but with a million-person cohort, they think they might be able to find out. "I guarantee that there would be tens of thousands of them taking [warfarin]," says Francis Collins, director of the National Institutes of Health. "With that many subjects, you'll be able to say, 'Well, actually it does look like it helps this subset, but they happened to have a diet that was this form instead of that form.'" Furthermore, he notes, one would be able to see the subtleties of why and how a treatment works or does not work.

One thing supporters and detractors of the new initiative agree on is that the challenges of such an undertaking will be mammoth. It will require integrating terabytes of existing health data, spread across scores of databases whose content and quality will vary widely. And it will involve storing blood and tissue samples from one million people—no small feat, especially if those samples are collected at regular intervals. If it succeeds—if scientists find reliable predictors of disease in that mass of data and then devise ways to treat individual patients by targeting those predictors—doctors will still need to become fluent in this new language. Most physicians are not trained to make sense of existing genetic tests, and so far no one has come up with a good way to train them.

In theory, personalized medicine could work like Netflix and Amazon.

In theory, personalized medicine could work like Netflix and Amazon. They know every book and movie you have bought in the past few years, and armed with that information, they can predict what you are likely to purchase next. If your doctors had that kind of information at their fingertips—not about your purchase history but about how you live, where you work, what your genetic predispositions are, and which microbes are populating your skin and gut—then maybe cures would finally come like movie recommendations do.

But it seems fair to say it will be a very long time before science gets to the point where it can offer individually tailored treatment to the masses, if it ever does. The question is, Should it even try? Although precision medicine might make sense for people with certain conditions that are difficult and expensive to treat, such as autoimmune diseases, critics argue that on the whole, simpler approaches to treating disease are better because they cost less and benefit far more patients. "Let's say we find a [targeted] drug that can lower risk of diabetes by two thirds," Paneth says. "It would cost about $150,000 [a year per person] for that drug if we had it. A simple program focused on diet and exercise will do the same. Life span has increased by about a decade in the past 50 years. And none of that gain is related to DNA. It's learning about smoking and diet and exercise. It's old-fashioned stuff."

In the end, this moon shot may make more sense as a research enterprise than a public health initiative. Scientists learn more every day about the distinct forces that interact to produce disease in individuals. It is natural and fitting that they should start putting that information together in a systematic way. But society should not expect such efforts to completely transform medicine any time soon. SA

SCIENTIFIC AMERICAN ONLINE
COMMENT ON THIS ARTICLE AT
SCIENTIFICAMERICAN.COM/APR2016

David Pogue is the anchor columnist for Yahoo Tech and host of several *NOVA* miniseries on PBS.

Dumb Design

Tech doesn't have to be confusing. Some simple changes could make digital media easier to use

By David Pogue

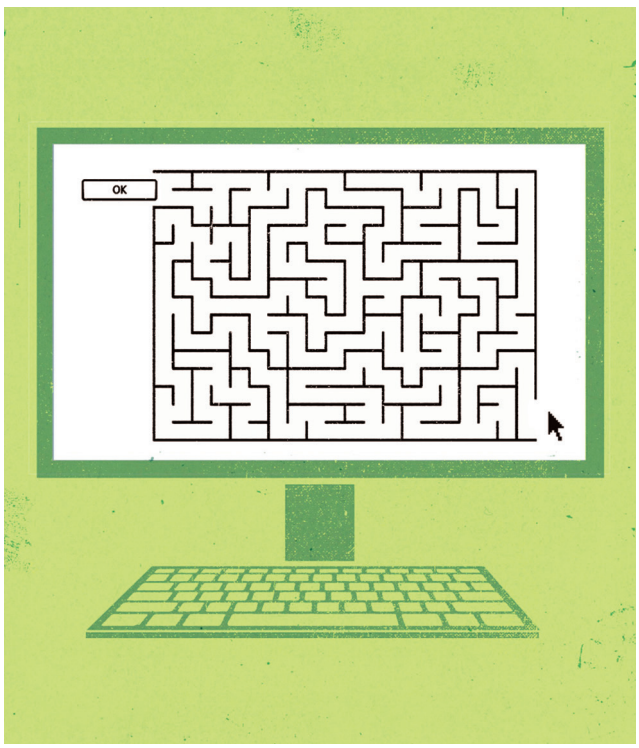
Have you ever tried to cancel a service on a company's Web page? You look everywhere, but you just can't find the Cancel option. It's almost as though the company has hidden it on purpose.

You've just experienced the power of interface design. And as more elements of our lives become computerized—cars, elevators, ovens, refrigerators—good and bad (and sneaky) interface design is going to matter more and more. The mobile era makes the challenge even greater; it's especially difficult to cram a lot of features into limited screen space.

At the moment, millions of people, stymied by terrible software design, blame themselves. "I must just be a dummy," they might mutter. "I guess I'm some kind of Luddite."

In fact, though, if a control doesn't work the way it should, or it isn't sitting where it ought to be, it may well be the designers' fault, not yours. It's time for interface design to enter the public dialogue, to matter just as much as price or customer service when we buy something.

Sometimes weird design choices are deliberate. It's no accident, for example, that a Web site's Sign Up button (for new customers) is almost always more prominent than the Sign In button (for existing customers).



But in other cases—many, many other cases—it seems clear that the creators of bad interface design just weren't thinking.

So today, in hopes of getting such a conversation going, I offer a few gentle suggestions for better software design. These are lessons for the designers, yes, but also for the rest of us—to use as a yardstick for assessing how well they've done their job.

Frequent features should be front and center. When you're filling in your address on a Web site, you're often asked to choose your country name from a menu. If you live in the U.S., you have to scroll past a couple of hundred countries in the alphabetical list!

The Internet is a global village. But by far the largest numbers of online visitors live in China, India and the U.S. Shouldn't their names appear at the top of the Country pop-up menu?

Better yet—why doesn't the Country field *know* the country you're in? (As Web advertising makes clear, it's trivial for a Web designer to figure that out.)

Consistency is secondary to frequency. Remember the PalmPilot pocket organizer? On its tiny screen, the address book app featured a prominent New button—and Delete was buried in a menu.

A Palm engineer explained to me why: Because new people enter your life a lot more often than they leave. You use Delete only when someone passes away, moves away or dumps you.

Step count matters. One click is always easier to learn and remember than several.

A classic example: If there are only two or three choices—say, Sleep, Restart and Shut Down—don't put them in a pop-up menu. Lay them all out on the screen; you have the room. Pop-up menus in general should be a last resort because nobody knows what options are *in* one until someone thinks to click it. And that's another step.

Words are crucial. Longtime geeks still chuckle at the infuriating ambiguity of the old Windows dialog boxes that had three buttons: Abort, Retry and Fail.

But guess what? Their descendants live on. To this day, I'd bet good money that lots of Windows users are confused by the choice of OK or Apply in dialog boxes—what's the difference?

Words matter in another way, too: A picture may be worth a thousand words but not when it's an unlabeled icon displaying a cryptic squiggle. Label your icons with words, people.

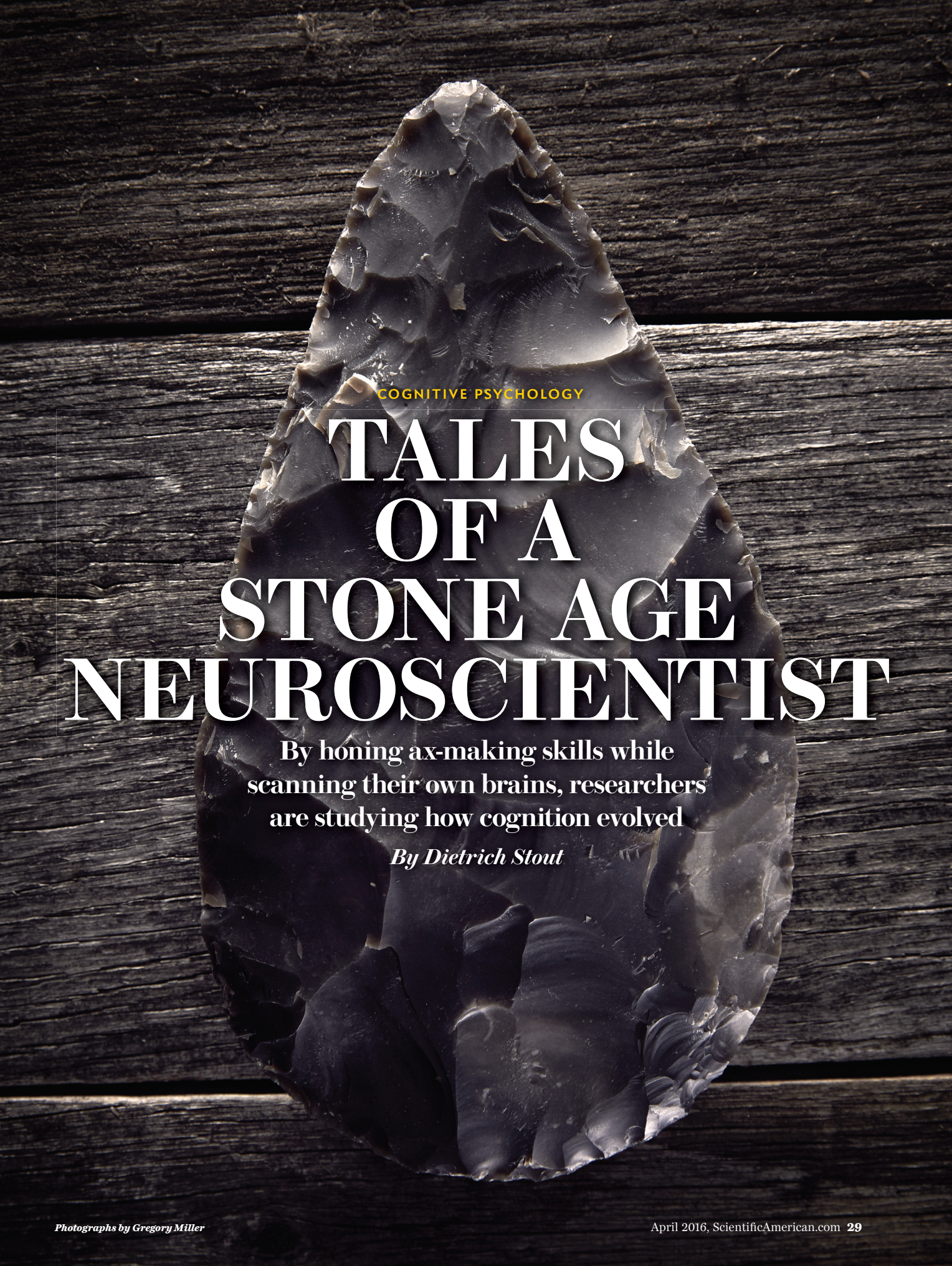
Many programmers are better at coding than writing—and that's fine. But someone who's better at writing than coding should have a look before the software goes final.

So there you have it: four pointers in the direction of better interface design. Next time you find yourself frustrated by a piece of technology, remember: let yourself off the hook. The fault may not be yours. SA

SCIENTIFIC AMERICAN ONLINE
GREAT INTERFACE DESIGN FAILURES:
SCIENTIFICAMERICAN.COM/APR2016/POGUE

Illustration by Richard Mia

TOOLMAKER: Anthropology professor Dietrich Stout works on a stone tool at Emory University's Paleolithic Technology Laboratory.



COGNITIVE PSYCHOLOGY

TALES OF A STONE AGE NEUROSCIENTIST

By honing ax-making skills while scanning their own brains, researchers are studying how cognition evolved

By Dietrich Stout

Photographs by Gregory Miller

Dietrich Stout is a professor of anthropology at Emory University. His research focus on Paleolithic stone toolmaking integrates experimental methods from diverse disciplines, ranging from archaeology to brain imaging.

I STILL HAVE THE FIRST STONE HAND AX I EVER MADE. IT'S A PRETTY POOR SPECIMEN, crudely chipped from a piece of frost-fractured flint I picked up on a walk through a farmer's field in West Sussex, England. It would not have impressed the human ancestors known to us as *Homo heidelbergensis*. These cousins of *Homo sapiens* from 500,000 years ago left much nicer hand axes at a nearby archaeological site in Boxgrove.

Still, I worked hard at making this simple cutting tool, and I am proud of it. What really matters, though, is not that I am dabbling in a new hobby. What matters is that my dabbling was intended to probe key questions of human evolution and the emergence of language and culture that are hallmarks of our species.

Replicating the skills of prehistoric peoples to understand human origins is not unprecedented—archaeologists have done it for decades. In the past 15 years, however, we have taken this approach in exciting new directions.

Working together, archaeologists and neuroscientists have brought brain-scanning machines to bear in observing what happens underneath the skull when a modern-day toolmaker chips away patiently at a stone, shaping it into a hand ax. With this view into the brain, we hope to identify which regions within may have evolved to help Paleolithic peoples chisel a well-crafted ax or knife from a formless hunk of rock.

These collaborations between archaeologists and neuroscientists have revived a largely discredited idea: that toolmaking was an important driver of the evolution of humans. British anthropologist Kenneth Oakley asserted 70 years ago in his influential book *Man the Tool-maker* that toolmaking was the "chief biological characteristic" of humanity that drove the evolution of our "powers of mental and bodily co-ordination."

The idea fell out of favor as behavioral scientists documented tool use and even toolmaking in nonhuman species such as apes, crows, dolphins and octopi. As paleontologist Louis Leakey put it in his now famous reply in 1960 to Jane Goodall's historic first report of chimpanzee tool use: "Now we must redefine tool, redefine Man, or accept chimpanzees as humans." For many scientists, complex social relationships replaced toolmaking as the central factor in primate brain evolution. In the 1980s and 1990s influential "Machiavellian intelligence" and "social brain" hypotheses argued that the greatest mental challenges primates face are in outsmarting other members of their own species, not in mastering their physical environment. These hypotheses gained empirical support from the observation that primate species that form large social groups also tend to have large brain sizes.

But more recent work, including our own, has shown that the "Man the Tool-maker" idea is not dead (although Oakley's language is clearly outdated). Toolmaking need not be unique to humans to have been important in our evolution. What matters is the kind of tools we make and how we learn to make them. Among primates, humans truly stand out in their ability to learn from one another. They are particularly adept at imitating what another person does. Mimicry is a prerequisite for learning complex technical skills and is thought to underlie the stunning ability of human culture to accumulate knowledge in a way that other apes do not. So it seems premature to abandon the idea that ancient stone tools might provide important information about human cognitive evolution. Teaching and learning increasingly complex toolmaking may even have posed a formidable enough challenge to our human ancestors that it spurred evolution of human language. In fact, many neuroscientists now believe that linguistic and manual skills both rely on some of the same brain structures.

To test these ideas, we have had to analyze carefully how an-

IN BRIEF

One way to answer questions about human evolution—and, in particular, the development of language and culture—entails replicating the skills used by prehistoric peoples.

A high-tech version of this approach uses brain-scanning machines to observe what neural regions become active when a toolmaker chips away at stone being shaped into a hand ax.

Crossover collaborations between archaeologists and neuroscientists have revived the largely discredited idea that the act of toolmaking served as a key driver of human evolution.

Teaching and learning the art of Stone Age toolmaking may, in fact, have posed a formidable enough challenge to our ancestors that it spurred the evolution of human language.

KNAPPING CLASS: Nada Khreisheh (*above, far right*) teaches hand-ax toolmaking 20 hours a week in the outdoor work area at Emory's Paleolithic Technology Laboratory. Each student receives a total of 100 hours of instruction. The flint hand ax (*right*) was the first such tool made by the author.

cient tools were made and compare these findings with evidence of the way relevant brain systems evolved. In studying these questions, we ran into immediate difficulties because neither brains nor behaviors appear in the fossil record. Given the paucity of evidence, our only recourse was to simulate in a laboratory setting the types of skills that were passed from generation to generation many millennia ago. For this reason, my students, collaborators and I have spent many years trying to emulate the skills of Paleolithic toolmakers.

EXPERIMENTAL ARCHAEOLOGY

USING MODERN BRAIN-SCANNING techniques to study some of humanity's oldest technologies may seem strange. We did get some funny looks when we first started wheeling carts of rocks into a state-of-the-art neuroimaging lab. But there is nothing startling about archaeologists performing experiments. Studying the present has long been one of the most important methods for understanding the past. Scientists have devised experiments to replicate ancient smelting techniques (archaeometallurgy) and to observe the relentless decay of animal carcasses (taphonomy) to better understand how they fossilize. Casual experiments in stone toolmaking—"knapping," as archaeologists call it—date back to the 19th century, and more controlled experiments are now well established in the study of lithic technology.

The scope of these experiments has grown in recent years. My graduate advisers—Nicholas Toth and Kathy Schick, both now at Indiana University Bloomington and the Stone Age Institute—proposed in 1990 using a then newly developed imaging technique to investigate what happens in the brain when making a Paleolithic tool. Following up on this initial idea during the past 15 years, I have made a major goal of my own research to figure out what happens inside the brain when a person knaps away at a piece of stone.

My lab now functions as something of an apprenticeship program in stone toolmaking. As I write, I can hear the tick, tick, tick of novice knappers adding yet more chips to a pile of broken flint in the work area outside my office at Emory University. Last

year that pile reached 10 feet across, measured five inches in height and contained more than 3,000 pounds of shattered rock. I watch through a window as postdoctoral researcher Nada Khreisheh leans over to offer advice to a frustrated student.

Khreisheh currently spends about 20 hours a week training 20 students (each receives 100 hours of instruction) in the ancient art of hand-ax-making. This is our most ambitious project to date. Every training session is video-recorded so we are able to later analyze which learning techniques work best. We collect and measure each finished artifact to track skill development. The students must undergo repeated magnetic resonance imaging to examine changing brain structure and function, as well as psychological tests to see if particular abilities, such as planning or short-term memory, may be linked to toolmaking aptitude. It is a huge amount of work but essential to understanding the subtleties of this prehistoric technology.

The neophyte must master a percussive technology so demanding that a small error can compromise the entire workpiece.

If nothing else, all this effort has taught us that making these tools is difficult. But what we want to know is why it is so hard. Oakley and other proponents of the "Man the Tool-maker" argument thought the key to toolmaking was a "uniquely human" ability for abstract thought—that is, the ability to imagine different kinds of tools as a kind of mental template to be reproduced. I respectfully disagree. As any experienced craftsperson might tell you, knowing what you want to make is not the hard part. The difficulty lies in actually making it.

Knapping a hand ax requires the neophyte craftsperson to master a percussive technology that involves using a handheld "hammer" of stone, bone or antler to chip flakes off a stone, shaping it into a useful tool. The work requires powerful blows, accurate to within a few millimeters, which are delivered too rapidly to allow for a midswing correction. Like chiseling a marble sculpture, each strike removes something that cannot be put back. Even small errors can compromise the entire workpiece.

Using a motion-tracking system, movement scientist Blandine Bril and her colleagues at the School for Advanced Studies in the Social Sciences in Paris have shown that, unlike novices, experienced knappers adjust the force of their blows to produce flakes of different sizes. Stringing together a series of such blows to achieve an abstract design goal such as a hand ax is achievable only after acquiring the necessary control through long and painstaking practice.

Our ancestors faced the same challenges when they learned to make stone tools, and their lives probably depended on success in doing so. The demands of toolmaking—combined with complex social interactions for teaching these skills—may have become driving forces for human cognitive evolution. We have labeled this modern reboot of Oakley's "Man the Tool-maker" hypothesis as *Homo artifex*—the Latin word *artifex* signifying skill, creativity and craftsmanship.

TOOLS ON THE BRAIN

TEACHING STUDENTS to work stone is not the only technical challenge in learning about prehistoric practices. Standard brain imaging does not lend itself to certain aspects of studying stone toolmaking. If you have ever had a scan in a MRI machine, you probably remember being told emphatically not to move because it would ruin the image. Unfortunately, lying motionless inside a two-foot-wide tube is not conducive to knapping, although you might be tempted to nap.

In our early experiments, we circumvented this problem by using a brain-imaging technique known as FDG-PET (fluorodeoxyglucose positron-emission tomography). The intravenous line to supply the radioactive molecule used in PET to image brain activity needs to be injected into the foot to allow knappers to use their hands, a somewhat painful procedure. The test subject can then freely chip away at the chunk of stone destined to become an ax or knife while the tracer is taken up in metabolically active tissues in the brain. After the subject is finished, we run a scan to determine where in the brain the chemical has accumulated.

Using this technique, I set out to investigate two Stone Age technologies—Oldowan and Late Acheulean—that bracket the beginning and end of the Lower Paleolithic, a critical evolutionary period from 2.6 million to 200,000 years ago when the brains of hominins (humans and their extinct ancestors) nearly tripled in size. The question we wanted to explore in my lab was whether the development of these technologies placed new demands on the brain that, over the millennia, might have led through natural selection to its expansion.

Oldowan toolmaking (named after Tanzania's Olduvai Gorge, where it was first described in the mid-20th century by paleoanthropologist-archaeologist team Louis and Mary Leakey) involves striking sharp flakes from a cobble core. These simple flakes of rock became humanity's first "knives." Conceptually, toolmaking does not get much simpler. But our early PET data confirmed that the actual knapping process still remains a demanding task that goes far beyond just simply striking rocks together.

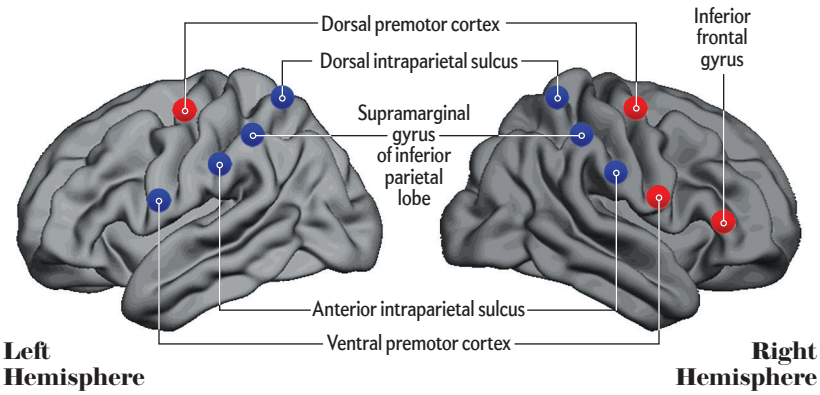
In our study, we allowed participants to practice for four hours without any instruction. As they became familiar with the task, they learned to identify and pay attention to particular features of the core, focusing, for instance, on areas that stuck out and would be easier to break. This learning is actually reflected in different patterns of activity in the visual cortex at the back of the brain before and after practice. But four hours' practice is not very long, even for humanity's earliest technology.

In truly experienced knappers, who can approximate the documented skills of real Oldowan toolmakers, something different is seen. As shown by Bril and her colleagues, experienced toolmakers distinguish themselves by their ability to control the amount of force applied during the percussive strike to detach flakes efficiently from the core. In the experts' brain, this skill

IMAGING

An Expansion of Brainpower

Scanning techniques reveal how more of the brain gets used as toolmaking becomes more sophisticated. Imaging distinguished areas activated when a modern toolmaker crafted an implement reminiscent of simple Oldowan tools (2.6 million to 1.6 million years ago) compared with regions active when making Acheulean hand axes (1.6 million to 200,000 years ago). Blue dots denote brain regions utilized when chiseling both Oldowan and Acheulean tools; red ones lit up as well when knapping an Acheulean hand ax.



spurred increased activity in the supramarginal gyrus in the parietal lobe, which is involved in awareness of the body's location in its spatial environment.

About 1.7 million years ago flake-based Oldowan technology began to be replaced by Acheulean technology (named after Saint-Acheul in France), which involved the making of more sophisticated tools, such as teardrop-shaped hand axes. Some Late Acheulean hand axes—those from the English site of Boxgrove that date back 500,000 years, for instance—were very finely shaped, with thin cross sections, three-dimensional symmetry and sharp, regular edges, all indicating a high level of knapping skill.

Modern knappers know that this technique requires not only precise control but carefully reasoned planning. Like a golfer selecting the right club, knappers use a variety of "hard" (stone) and "soft" (antler/bone) hammers as they work through planned flaking sequences that prepare core edges and surfaces to fracture in the desired pattern. They must switch back and forth between different subtasks while keeping the overall goal of a finished ax firmly in mind, resisting the temptation to take shortcuts. I know from bitter experience that you can't cheat the physics of stone fracture. It is better to just quit for the day when you are tired or frustrated.

The demands of knapping a Late Acheulean tool also produce a characteristic signature in the brain scanner. Some of the same areas are involved in both Oldowan and Acheulean knapping. But our Acheulean PET data also show activation extending into a specific region of the prefrontal cortex, called the right inferior frontal gyrus. Decades of research by neuroscientists such as Adam Aron of the University of California, San Diego, have linked this region to the cognitive control needed to switch between different tasks and to hold back inappropriate responses.

We have since corroborated our PET results by using MRI, which provides higher-resolution imaging. To do this, we had to figure out a way to keep subjects immobilized. Working with social neuroscientist Thierry Chaminade, now at the Institute of Neurosciences of Timone at Aix-Marseille University in France, I asked subjects to lie still in the scanner and watch knapping videos rather than actually trying to make tools. This approach works because, as Chaminade and many others have shown, we use many of the same brain systems to understand observed actions as we do to execute them. Despite different methodologies, we found the same responses in the brain's visuomotor areas for both Oldowan and Acheulean knapping—and increased activity in the right inferior frontal gyrus when subjects watched the crafting of Late Acheulean tools.

We concluded that the ability to learn demanding physical skills would have been important to early Oldowan stages of human technological evolution but that Acheulean methods also required an enhanced level of cognitive control furnished by the prefrontal cortex. In fact, this observation agreed fairly well with the fossil evidence, which shows that some of the fastest increases in brain size over the past two million years occurred during the Late Acheulean. But that discovery did not establish which event was a cause and which was a consequence. Did toolmaking actually drive brain evolution in *H. artifex,* or did it simply come along for the ride? To address this question, we needed to get even more serious about studying how the brain learns to make tools.

LEARNING AND EVOLUTION

IT TOOK ME about 300 hours of practice to equal the skills of the Late Acheulean toolmakers at Boxgrove. The learning process might have gone quicker if I had worked with a teacher or been part of a toolmaking community. But I am not really certain. Despite decades of experimental knapping, almost no systematic studies of the learning process have been conducted. In 2008 Bruce Bradley, a professor of archaeology at the University of Exeter in England and a longtime experimental knapper, invited me to address that gap in our knowledge. Bradley wanted to train the next generation of British academic knappers, and he thought I might like to collect some neuroimaging data along the way to gain better insight into the learning process. He was right—I did.

One thing that I was particularly excited to try was a relatively new technique called diffusion tensor imaging (DTI), a form of MRI that allows scientists to map the white matter fiber tracts that serve as the brain's "wiring." In 2004 a group led by Bogdan Draganski, then at the University of Regensburg in Germany, used DTI to show structural changes in the brains of volunteers learning to juggle, which challenged the traditional view that the structure of adult brains is relatively fixed.

We suspected that learning to knap would also require some degree of neural rewiring. If so, we wanted to know which circuits were affected. If our idea was correct, we hoped to get a

COURTESY OF THIERRY CHAMINADE, *Institute of Neurosciences of Timone, Aix-Marseille University*

CHIPS OFF THE BLOCK: A novice toolmaker knapped a flint hand ax, surrounded here by flakes detached while making the implement. Each piece is labeled, weighed and measured so that the process of learning motor and planning skills can be analyzed in detail.

glimpse of whether toolmaking can actually cause, on a small scale, the same type of anatomical changes in an individual that occurred over the course of human evolution.

The answer turned out to be a resounding yes: practice in knapping enhanced white matter tracts connecting the same frontal and parietal regions identified in our PET and MRI studies, including the right inferior frontal gyrus of the prefrontal cortex, a region critical for cognitive control. The extent of these changes could be predicted from the actual number of hours each subject spent practicing—the more someone practiced, the more their white matter changed.

Brain changes—what neuroscientists term "plasticity"—provide raw material for evolutionary change, an effect known as phenotypic accommodation. Plasticity allows species the flexibility to try out new behaviors—to "push the envelope" of their current adaptation. If they happen to discover a good trick, it enters their behavioral repertoire, and the evolutionary race is on: natural selection will favor any variations that enhance the ease, efficiency or reliability of learning the new trick. Our result thus provided important evidence that the idea of *H. artifex* was viable—and that toolmaking *could* actually have driven brain change through known evolutionary mechanisms.

With that information in hand, we needed to know next whether the anatomical responses we had observed paralleled specific evolutionary developments in the human brain. Fossil skulls cannot provide detailed information about changes to internal brain structures, so we turned to the next best thing: a direct comparison with one of our closest living relatives, the chimpanzee.

Fortunately, I had already enlisted the assistance of Erin Hecht, a recent Emory Ph.D., now at Georgia State University, to assist with the DTI analyses. Hecht's dissertation work comparing chimpanzee and human neuroanatomy had given her access to precisely the data and expertise we needed. The result, published last year, was a DTI-based virtual dissection of white matter tracts in the two species that would identify any differences in the relevant brain circuits. It confirmed what we had suspected: the toolmaking circuits identified in our PET, MRI and DTI studies were indeed more extensive in humans than in chimps, especially when it came to connections to the right inferior frontal gyrus. This finding became the final link in a chain of inferences from ancient artifacts to behavior, cognition and brain evolution that I had been assembling since my days as a graduate student in the late 1990s. It provides powerful new support for the old idea that Paleolithic toolmaking helped to shape the modern mind. It is far from the end of the story, however.

THROUGH THE KEYHOLE

I LOVE STONE TOOLS, but they provide us with only the narrowest keyhole view of the complex lives of our ancestors. Like a geologist with a seismograph, the trick is to turn these bits of knowledge from the neuroscience of toolmaking into a rich model of Stone Age existence.

Although the evidence from stone tools is limited, we could have done worse. Stone toolmaking takes as much time to learn as many academic skills: a typical American college class is supposed to require about 150 hours of work (10 hours a week over a 15-week semester). In the study with Bradley, trainees logged an average of 167 hours' practice and were still struggling with Acheulean hand-ax-making by the end. Perhaps I should not feel too bad about the 300 hours it took me to learn. But sticking to such a tedious and frustrating practice regimen requires motivation and self-control, both intriguing attributes from an evolutionary perspective.

Motivation can come externally from a teacher or internally from the anticipation of a future reward. Many researchers have considered teaching to be the defining feature of human culture, whereas anticipating the future is clearly vital to everything from social relationships to technical problem solving.

Of course, motivational "carrots" take you only so far without the "stick" of self-control. The ability to exercise self-control—the inhibition of counterproductive impulses—is critical to many kinds of cognitive skills. In fact, a recent study led by Evan MacLean of Duke University found self-control and future planning to be correlated with larger brain size across 36 species of birds and mammals. Our own work has now resulted in an accumulation of evidence that ties successful hand-ax-making to brain systems for self-control and future planning—providing a direct link with this comparative evidence of brain-size evolution across species.

Besides demonstrating motivation and self-control, the toolmaker must achieve a depth of understanding about the characteristics of the stone being worked that is very difficult to obtain through self-teaching. The learning curve for knapping follows a staircase pattern: most of the time you just need to practice and consolidate skills, but every once in a while, a bit of advice takes you to the next level. Although it is sometimes possible to discover tricks of the trade of stone toolmaking independently, there is a real advantage to learning from others.

One good way to learn is simply to watch. Although calling someone a good imitator can be taken as an insult, comparative psychologists have come to recognize faithful copying as a pillar of human culture. Work by Andrew Whiten of the University of St. Andrews in Scotland and many others has shown that apes have some ability to imitate but nowhere near the compulsive, high-fidelity copying skills of human children and adults.

Is imitation on its own enough? You might be able to figure out chess by watching enough games, but it would be a lot easier if someone explained the nuances of strategy and tactics. What we want to know is whether this is also true of stone toolmaking and other prehistoric skills. Thomas Morgan of the University of California, Berkeley, and his colleagues recently conducted a stone-toolmaking experiment to examine how knowledge passes from one person to the next. They showed a significant learning advantage when teaching used language instead of simply demonstrating a skill. Further experiments along these lines might one day help answer the great mystery of when and why human language evolved.

Teaching is not the only possible connection between toolmaking and language. Neuroscientists recognize that most regions of the human brain perform basic computations related to a variety of different behaviors. Take, for instance, 19th-century anthropologist Paul Broca's classic "speech" area in the left inferior frontal gyrus.

Since the 1990s new research has shown that Broca's area contributes not just to speech but to music, mathematics and the understanding of complex manual actions. This recognition has reinvigorated the long-standing idea that toolmaking, along with the human propensity to communicate through gestures, may have served as pivotal evolutionary precursors to language. This idea has been most fully developed by Michael A. Arbib of the University of Southern California, for example, in his 2012 book *How the Brain Got Language*.

Imaging studies hint that neural circuits used in toolmaking were co-opted by the brain for primitive forms of communication.

The results of our own imaging studies on stone toolmaking led us recently to propose that neural circuits, including the inferior frontal gyrus, underwent changes to adapt to the demands of Paleolithic toolmaking and then were co-opted to support primitive forms of communication using gestures and, perhaps, vocalizations. This protolinguistic communication would then have been subjected to selection, ultimately producing the specific adaptations that support modern human language. Our ongoing experiments, aside from building a massive mound of broken flint, will allow us to put this hypothesis to the test. SA

MORE TO EXPLORE

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Dietrich Stout's publications: **https://scholarblogs.emory.edu/stoutlab/publications**

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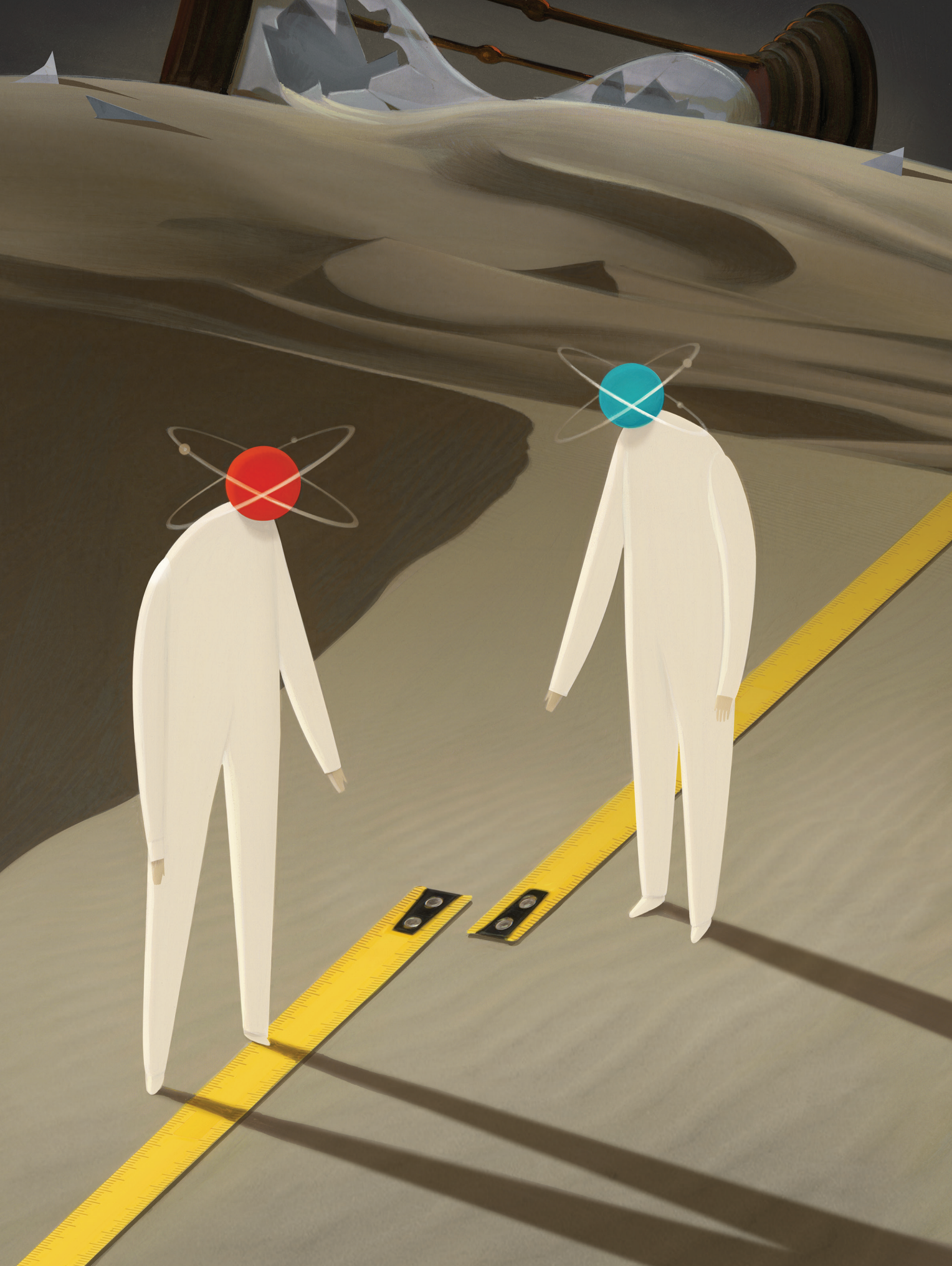


PARTICLE PHYSICS

the neutron enigma

Two precision experiments disagree on how long neutrons live before decaying. Does the discrepancy reflect measurement errors or point to some deeper mystery?

By Geoffrey L. Greene and Peter Geltenbort

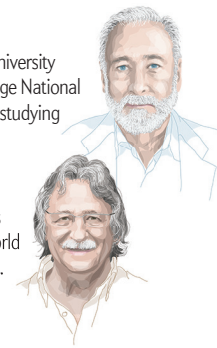
IN BRIEF

The best experiments in the world cannot agree on how long neutrons live before decaying into other particles.
Two main types of experiments are under way: bottle traps count the number of neutrons that survive after various intervals, and beam experiments look for the particles into which neutrons decay.
Resolving the discrepancy is vital to answering a number of fundamental questions about the universe.

Illustration by Bill Mayer

Geoffrey L. Greene is a professor of physics at the University of Tennessee, with a joint appointment at the Oak Ridge National Laboratory's Spallation Neutron Source. He has been studying the properties of the neutron for more than 40 years.

Peter Geltenbort is a staff scientist at the Institut Laue-Langevin in Grenoble, France, where he uses one of the most intense neutron sources in the world to research the fundamental nature of this particle.



LUCKILY FOR LIFE ON EARTH, MOST MATTER IS NOT RADIOACTIVE. WE TAKE THIS FACT FOR granted, but it is actually somewhat surprising because the neutron, one of the two components of atomic nuclei (along with the proton), is prone to radioactive decay. Inside an atomic nucleus, a typical neutron can survive for a very long time and may never decay, but on its own, it will transform into other particles within 15 minutes, more or less. The words "more or less" cover a disturbing gap in physicists' understanding of this particle. Try as we might, we have not been able to accurately measure the neutron lifetime.

This "neutron lifetime puzzle" is not just embarrassing for us experimentalists; resolving it is vital for understanding the nature of the universe. The neutron decay process is one of the simplest examples of the nuclear "weak" interaction—one of nature's four fundamental forces. To truly understand the weak force, we must know how long neutrons live. Furthermore, the survival time of the neutron determined how the lightest chemical elements first formed after the big bang. Cosmologists would like to calculate the expected abundances of the elements and compare them with astrophysical measurements: agreement would confirm our theoretical picture, and discrepancy could indicate that undiscovered phenomena affected the process. To make such a comparison, however, we need to know the neutron lifetime.

More than 10 years ago two experimental groups, one a Russian-led team in France and the other a team in the U.S., attempted separately to precisely measure the lifetime. One of us (Geltenbort) was a member of the first team, and the other (Greene) was a member of the second. Along with our colleagues, we were surprised and somewhat disturbed to find that our results disagreed considerably. Some theoreticians suggested that the difference arose from exotic physics—that some neutrons in the experiments might have transformed into particles never before detected, which would have affected the different experiments in divergent ways. We, however, suspected a more mundane reason—perhaps one of our groups, or even both, had simply made a mistake or, more likely, had overestimated the accuracy of its experiment. The U.S. team recently completed a long, painstaking project to study the most dominant source of uncertainty in its experiment in hopes of resolving the discrepancy. Rather than clearing up the situation, that effort confirmed our earlier result. Similarly, other researchers later confirmed the findings of Geltenbort's team. This discrepancy has left us even more perplexed. But we are not giving up—both groups and others continue to seek answers.

TIMING NEUTRONS

IN THEORY, measuring the neutron lifetime should be straightforward. The physics of nuclear decay are well understood, and we have sophisticated techniques for studying the process. We know, for instance, that if a particle has the possibility of transforming into a lower-mass particle or particles while conserving such characteristics as charge and spin angular momentum, it will. Free neutrons display this instability. In a process called beta decay, a neutron breaks up into a proton, an electron and an antineutrino (the antimatter counterpart of the neutrino), which collectively sum to a slightly lower mass but the same total charge, spin angular momentum and other conserved properties. These conserved properties include "mass-energy," meaning that the daughter particles carry the difference in mass in the form of kinetic energy, the energy of motion.

We cannot predict exactly when a particular neutron will decay because the process is a fundamentally random quantum phenomenon—we can say only how long neutrons live on average. Thus, we must measure the average neutron lifetime by studying the decay of many neutrons.

Investigators have employed two experimental methods—one called the "bottle" technique and the other the "beam" approach. Bottle experiments confine neutrons in a container and count how many are left after a given time. The beam method, in contrast, looks not for the disappearance of neutrons but rather for the appearance of the particles into which they decay.

The bottle approach is particularly challenging because neutrons can pass easily through matter and thus through the walls of most containers. Following a suggestion first explicitly made by Russian physicist Yuri Zel'dovich, experimentalists who use the bottle approach—as Geltenbort and his colleagues in France do—get around the problem by trapping extremely cold neutrons (that is, those with a very low kinetic energy) within a container of very smooth walls [*see box on page 40*]. If the neutrons are slow enough and the bottle smooth enough, they reflect from the walls and hence remain in the bottle. To achieve this effect, the neutrons must move at speeds on the order of just a few meters per second, as opposed to the roughly 10 million meters per second neutrons travel when emitted during nuclear fission, for instance. These "ultracold" neutrons are so slow that you could "outrun"

them. The most accurate bottle experiment to date took place at the Institut Laue-Langevin (ILL) in Grenoble, France.

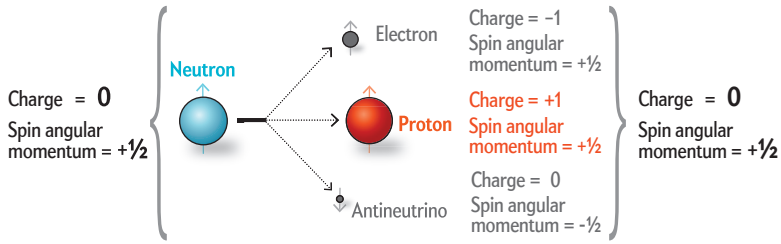
Unfortunately, no bottle is ever perfect. If neutrons occasionally leak out of the bottle, we will attribute this loss to beta decay and will get the wrong lifetime. We must therefore be sure to correct our calculations so as to count only those particles that actually undergo beta decay.

To make that correction, we use a clever technique. The number of neutrons lost through the walls of the bottle depends on the rate at which neutrons bounce against the walls. If the neutrons are slower or the bottle is bigger, the bounce rate, and thus the loss rate, will go down. By varying both the size of the bottle and the energy (velocity) of the neutrons in successive trials, we can extrapolate to a hypothetical bottle in which there are no collisions and thus no wall losses. Of course, this extrapolation is not perfect, but we do our best to account for any error this calculation introduces.

BASICS

How Neutrons Decay

Despite decades of trying, scientists have not been able to definitively measure how long neutrons live outside of atomic nuclei—the best experiments in the world produce conflicting results. Although the length of the neutron lifetime is undetermined, the cause of neutron decay is well known. Through a process called beta decay, a neutron transforms into a proton and releases an electron and an antineutrino, the antimatter counterpart to the neutrino particle. The decay ensures that the final particles' charge and spin angular momentum tally to equal those of the original particle.



In the beam method—used by Greene and others at the National Institute of Standards and Technology (NIST) Center for Neutron Research—we send a stream of cold neutrons through a magnetic field and a ring of high-voltage electrodes that traps positively charged particles [*see box on page 41*]. Because neutrons are electrically neutral, they pass right through the trap. If, however, a neutron decays within the trap, the resulting positively charged proton gets "stuck." Periodically we "open" the trap and expel and count the protons. In principle, the proton trapping and detection are nearly perfect, and we must make only very small corrections for the possibility that we missed decays.

WHERE COULD WE GO WRONG?

TO BE USEFUL, a measurement must be accompanied by a reliable estimate of its accuracy. A measurement of a person's height that has an uncertainty of one meter, for example, is much less meaningful than a measurement that has an uncertainty of one millimeter. For this reason, when we make precision measurements we always report an experimental uncertainty; an uncertainty of one second, for instance, would mean our measurement had a high probability of being no more than a second shorter or a second longer than the true value.

Any measurement has, in general, two sources of uncertainty. Statistical error arises because an experiment can measure only a finite sample—in our case, a finite number of particle decays. The larger the sample, the more reliable the measurement and the lower the statistical error.

The second source of uncertainty—systematic error—is much more difficult to estimate because it arises through imperfections in the measurement process. These flaws may be something simple, like a poorly calibrated meter stick used to measure a person's height. Or they can be more subtle, like a sampling bias—in a telephone poll, for example, one might overly rely on calls to land lines rather than to cell phones and thus fail to capture a truly representative population sample. Experimentalists go to great lengths to reduce these systematic errors, but they are impossible to eradicate completely. The best we can do is carry out a detailed study of all imaginable sources of error and then estimate the lingering effect each might have on the final result. We then add this systematic error to the statistical error to give a best estimate of the overall reliability of the measurement. In other words, we put great effort into estimating the "known unknowns."

Of course, our great fear is that we have overlooked an "unknown unknown"—a systematic effect that we do not even know we do not know—hidden within the experimental procedure. While we go to extreme pains to explore all possible uncertainties, the only way to overcome this type of additional error with real confidence is to perform another, completely independent measurement using a totally different experimental method that does not share the same systematic effects. If two such measurements agree within their quoted uncertainties, we have confidence in the results. If, on the other hand, they disagree, we have a problem.

For the measurement of the neutron lifetime we have two such independent methods: the beam and the bottle. The most recent result from the beam experiment at NIST gave a value for the neutron lifetime of 887.7 seconds. We determined the statistical uncertainty in our estimate to be 1.2 seconds and the systematic uncertainty 1.9 seconds. Combining those errors statistically gives a total uncertainty of 2.2 seconds, which means that we believe the true value of the neutron lifetime has a 68 percent probability of being within 2.2 seconds of the measured value.

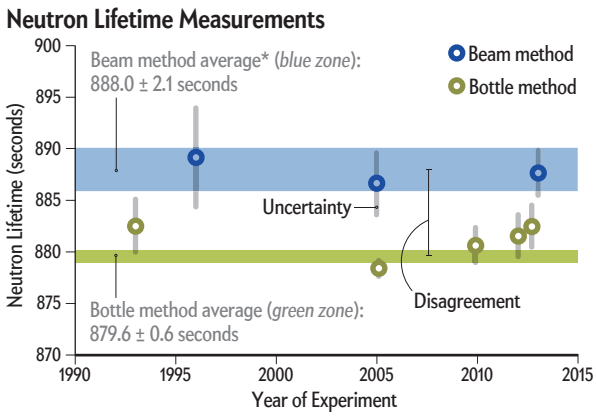
The bottle experiment at ILL, on the other hand, measured a neutron lifetime of 878.5 seconds with a statistical uncertainty of 0.7 second, a systematic uncertainty of 0.3 second and a total uncertainty of 0.8 second.

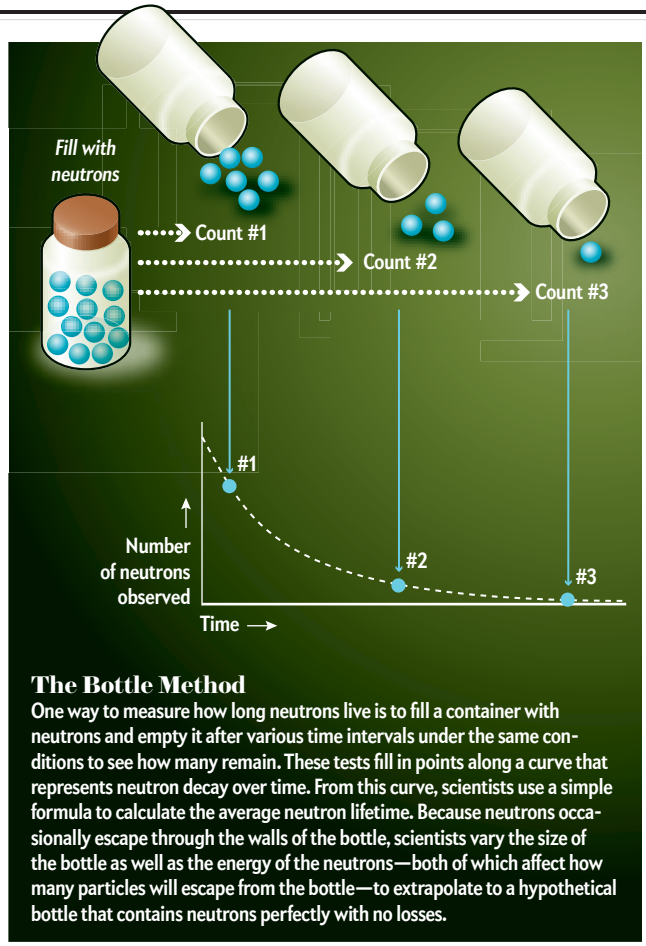
These are the two most precise neutron lifetime experiments of each type in the world, and their measurements differ by approximately nine seconds. Such a time span may not sound like a lot, but it is significantly larger than the calculated uncertainties for both experiments—the probability of obtaining a

Graphics by Nigel Hawtin

Different Techniques, Different Results

Scientists have tried two main techniques to measure the average neutron lifetime: the "bottle" and the "beam" methods. The various bottle measurements over the years tend to agree with one another within their calculated error bars, as do the beam measurements. The results from the two techniques, however, conflict. The discrepancy, about eight seconds between the bottle and beam averages, may not seem like much, but it is significantly larger than the measurements' uncertainty, which means the divergence represents a real problem. Either the researchers have underestimated the uncertainty of their results, or, more exciting, the difference arises from some unknown physical phenomenon.





The Bottle Method
One way to measure how long neutrons live is to fill a container with neutrons and empty it after various time intervals under the same conditions to see how many remain. These tests fill in points along a curve that represents neutron decay over time. From this curve, scientists use a simple formula to calculate the average neutron lifetime. Because neutrons occasionally escape through the walls of the bottle, scientists vary the size of the bottle as well as the energy of the neutrons—both of which affect how many particles will escape from the bottle—to extrapolate to a hypothetical bottle that contains neutrons perfectly with no losses.

*The beam method average does not include the 2005 measurement, which was superseded by the 2013 beam study.

difference of this size by chance alone is less than one part in 10,000. We must therefore seriously consider the possibility that the discrepancy results from an unknown unknown—we have missed something important.

EXOTIC PHYSICS

AN EXCITING explanation for the difference could be that it actually reflects some exotic physical phenomenon not yet discovered. A reason to think such a phenomenon might exist is that although the bottle and beam methods disagree, other beam studies show good agreement among themselves, as do other bottle studies.

Imagine, for example, that in addition to the regular beta decay, neutrons decayed via some previously unknown process that does not create the protons sought in beam experiments. The bottle experiments, which count the total number of "lost" neutrons, would count both the neutrons that disappeared via beta decay as well as those that underwent this second process. We would therefore conclude that the neutron lifetime was shorter than that from "normal" beta decay alone. Meanwhile the beam experiments would dutifully record only beta decays that produce protons and would thus result in a larger value for the lifetime. So far, as we have seen, the beam experiments do measure a slightly longer lifetime than the bottles.

A few theorists have taken this notion seriously. Zurab Berezhiani of the University of L'Aquila in Italy and his colleagues have suggested such a secondary process: a free neutron, they propose, might sometimes transform into a hypothesized "mirror neutron" that no longer interacts with normal matter and would thus seem to disappear. Such mirror matter could contribute to the total amount of dark matter in the universe. Although this idea is quite stimulating, it remains highly speculative. More definitive confirmation of the divergence between the bottle and beam methods of measuring the neutron lifetime is necessary before most physicists would accept a concept as radical as mirror matter.

Much more likely, we think, is that one (or perhaps even both) of the experiments has underestimated or overlooked a systematic effect. Such a possibility is always present when working with delicate and sensitive experimental setups.

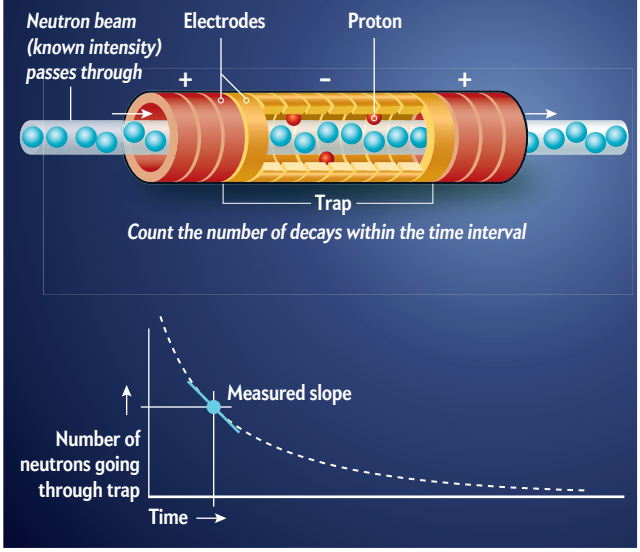
WHY THE NEUTRON LIFETIME MATTERS

FIGURING OUT WHAT WE MISSED will of course give us experimentalists peace of mind. But even more important, if we can get to the bottom of this puzzle and precisely measure the neutron lifetime, we may be able to tackle a number of long-standing, fundamental questions about our universe.

First of all, an accurate assessment of the timescale of neutron decay will teach us about how the weak force works on other particles. The weak force is responsible for nearly all radioactive decays and is the reason, for instance, that nuclear fusion occurs within the sun. Neutron beta decay is one of the simplest and most pure

The Beam Method

In contrast to the bottle method, the beam technique looks not for neutrons but for one of their decay products, protons. Scientists direct a stream of neutrons through an electromagnetic "trap" made of a magnetic field and ring-shaped high-voltage electrodes. The neutral neutrons pass right through, but if one decays inside the trap, the resulting positively charged protons will get stuck. The researchers know how many neutrons were in the beam, and they know how long they spent passing through the trap, so by counting the protons in the trap they can measure the number of neutrons that decayed in that span of time. This measurement is the decay rate, which is the slope of the decay curve at a given point in time and which allows the scientists to calculate the average neutron lifetime.



examples of a weak force interaction. To calculate the details of other, more complex nuclear processes involving the weak force, we must first fully understand how it operates in neutron decay.

Discerning the exact rate of neutron decay would also help test the big bang theory for the early evolution of the cosmos. According to the theory, when the universe was about one second old, it consisted of a hot, dense mixture of particles: protons, neutrons, electrons, and others. At this time, the temperature of the universe was roughly 10 billion degrees—so hot that these particles were too energetic to bind together into nuclei or atoms. After about three minutes, the universe expanded and cooled to a temperature where protons and neutrons could stick together to make the simplest atomic nucleus, deuterium (the heavy isotope of hydrogen). From here other simple nuclei were able to form—deuterium could capture a proton to make an isotope of helium, two deuterium nuclei could join together to create heavier helium, and small numbers of larger nuclei formed, up to the element lithium (all the heavier elements are thought to have been produced in stars many millions of years later).

This process is known as big bang nucleosynthesis. If, while the universe was losing heat, neutrons had decayed at a rate that was much faster than the universe cooled, there would have been no neutrons left when the universe reached the right temperature to form nuclei—only the protons would have remained, and we would have a cosmos made almost entirely of hydrogen. On the other hand, if the neutron lifetime were much longer than the time required to cool sufficiently for big bang nucleosynthesis, the universe would have an overabundance of helium, which in turn would have affected the formation of the heavier elements involved in the evolution of stars and ultimately life. Thus, the balance between the universal cooling rate and the neutron lifetime was quite critical for the creation of the elements that make up our planet and everything on it.

From astronomical data we can measure the cosmic ratio of helium to hydrogen, as well as the amounts of deuterium and other light elements that exist throughout the universe. We would like to see if these measurements agree with the numbers predicted by big bang theory. The theoretical prediction, however, depends on the precise value of the neutron lifetime. Without a reliable value for it, our ability to make this comparison is limited. Once the neutron lifetime is known more precisely, we can compare the observed ratio from astrophysical experiments with the predicted value from theory. If they agree, we gain further confidence in our standard big bang scenario for how the universe evolved. Of course, if they disagree, this model might have to be altered. For instance, certain discrepancies might indicate the existence of new exotic particles in the universe such as an extra type of neutrino, which could have interfered in the process of nucleosynthesis.

One way to resolve the difference between the beam and bottle results is to conduct more experiments using methods of comparable accuracy that are not prone to the same, potentially confounding systematic errors. In addition to continuing the beam and bottle projects, scientists in several other groups worldwide are working on alternative methods of measuring the neutron lifetime. A group at the Japan Proton Accelerator Research Complex (J-PARC) in Tokai is developing a new beam experiment that will detect the electrons rather than protons produced when neutrons decay. In another very exciting development, groups at ILL, the Petersburg Nuclear Physics Institute in Russia, Los Alamos National Laboratory, the Technical University of Munich and the Johannes Gutenberg University Mainz in Germany plan to use neutron bottles that confine ultracold neutrons with magnetic fields rather than material walls. This is possible because the neutron, though electrically neutral, behaves as though it is a small magnet. The number of neutrons accidentally lost through the sides of such bottles should be quite different from that of previous measurements and thus should produce quite different systematic uncertainties. We fervently hope that, together, continuing bottle and beam experiments and this next generation of measurements will finally solve the neutron lifetime puzzle. SA

MORE TO EXPLORE

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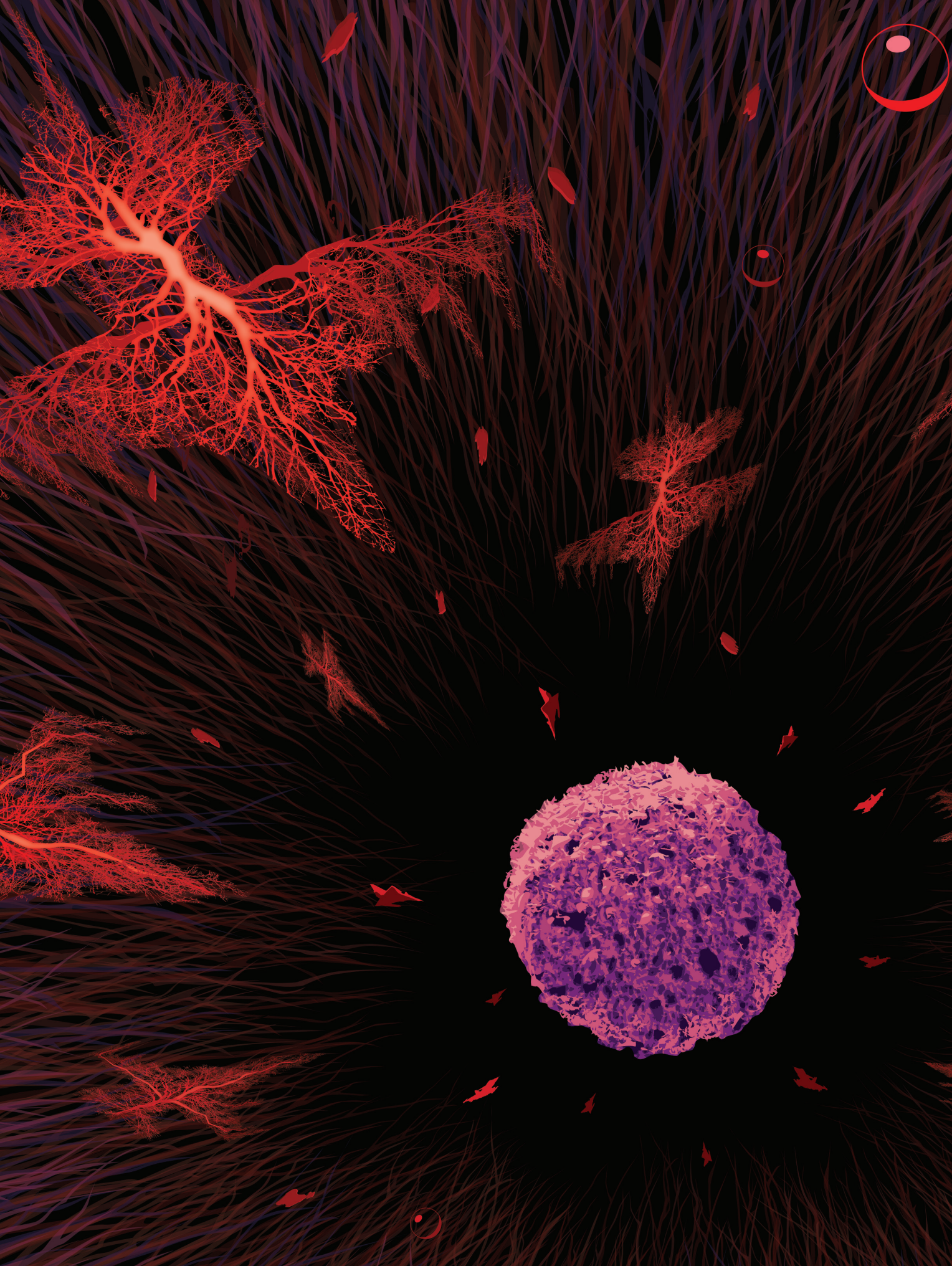
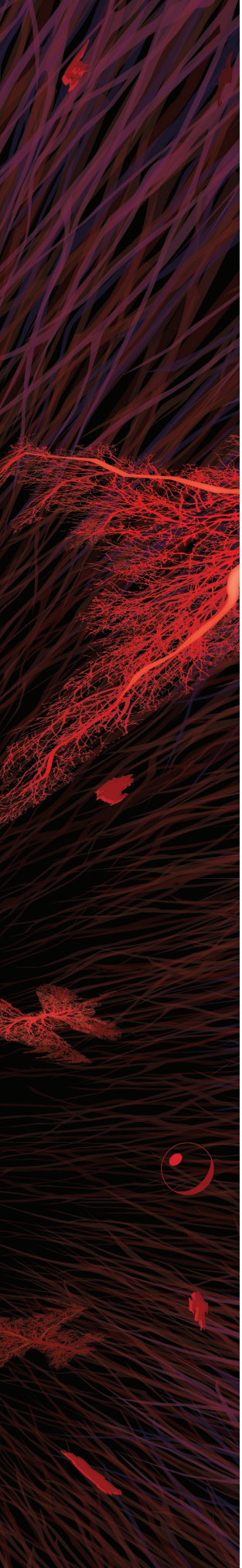




2016 FUTURE OF MEDICINE

THE CANCER DEFENSE

Enhancing the body's own immune system is leading to promising results in the battle against malignancy

By Karen Weintraub

IN BRIEF

A new generation of treatments that boost the immune system's ability to fight and control malignant cells indefinitely have achieved remarkable results over the past five years.

Thousands of people with aggressive and advanced lung and skin cancers, as well as various kinds of leukemia and lymphoma, have been treated—and many of them have seemingly been cured.

Investigators are developing new regimens and combinations of treatments that may prove safer and more effective than current approaches in the next few years.

Illustration by Daniel Hertzberg

IF MICHELLE BOYER had received her diagnosis of advanced and aggressive skin cancer in 2010 instead of 2013, she would almost certainly be dead by now. Melanoma, the most lethal form of skin malignancy, had spread from a mole on her back to her lungs, and she knew her prognosis was grim. But beginning in May 2013, the 29-year-old Seattle resident started a series of revolutionary treatments—some of which first became available in 2011—that prompted her immune system to identify, attack and shrink the tumors. Although Boyer still has cancer and the immune-boosting drugs have taken a toll on her body, she is grateful to be alive and hopes that either her current course of therapy or the next one will eventually give her the kind of miraculous results that other patients have talked about on the Internet. "At this point, this is my life," she says. "People think it would be really hard to stay positive, but because to me it seems normal, it's not as much effort as you would think."

Karen Weintraub is a freelance health and science journalist who writes regularly for STAT (www.statnews.com), *USA Today* and the *New York Times*, among others.

Karen Koehler, 59, a retired special education teacher from Park Ridge, N.J., may have won the immunotherapy jackpot on her first try. She has apparently been cured of a different kind of cancer—in her case leukemia—after a single infusion, in early 2015, with some of her own immune cells that had been genetically altered to fight her malignancy more aggressively. The treatment, which lasted a couple of hours, landed her in intensive care for several days because her revved-up immune system shifted so far into overdrive. This setback was followed by weeks in a regular hospital bed. But within a month after her treatment, scans showed no signs of cancer anywhere in her body.

Boyer and Koehler are two of the thousands of cancer patients who have undergone various kinds of immunotherapy over the past five years. Their experiences illustrate both the promise and the challenges of this fundamentally new approach to treating cancer—one that, instead of dousing the body with toxic chemicals or radiation from the outside to kill cancer cells, energizes the complex and highly interactive cells and molecular signals of its defense networks to do the job from the inside. The results so far have been encouraging; immunotherapy is quickly becoming a pillar—along with surgery, radiation and chemotherapy—of treatment for some cancers.

In clinical trials of a new immunotherapy for a highly aggressive form of leukemia, 90 percent of patients underwent a complete remission: doctors could find no evidence of their disease anywhere in their bodies. Although some may eventually suffer a return of their cancer, for many others the response appears to be a permanent cure. In other trials, more than half of patients with advanced melanoma who received immunotherapy can now count their life expectancy in years instead of months. Immunotherapy, says Gary Gilliland, president and director of the Fred Hutchinson Cancer Research Center in Seattle, "is truly paradigm shifting in our approach to treating cancer."

These are, admittedly, still early days. Increasing life expectancy to a few years for some cancers still means that patients die of the disease. So scientists continue to experiment with different ways to unleash and boost the immune response, including vaccines, viruses, genetically engineered cells and pills [*see boxes on pages 46 and 50*]. They are also beginning to combine these approaches to see if they can help more patients, perhaps with fewer side effects. But there is no longer any doubt that physicians can tap the immune system to beat cancer at least some of the time. "[We are at] the end of the beginning" of the immunotherapy story, says Eric Rubin, vice president of global clinical oncology for Merck Research Laboratories.

LIQUID SUCCESS

THE DREAM of fighting cancer with the immune system dates back at least 125 years to William Coley of New York City, a physician who injected some of his cancer patients with bacteria in an effort to jump-start their body's natural healing powers. Coley's approach was taken up by a few other doctors initially. But it gradually fell out of favor after his death in 1936, to be replaced by advances in chemotherapy and later hormone and antibody treatments, which showed more consistent results on a larger number of patients.

The idea of boosting the immune system, however, has never entirely lost its appeal, promoted in part by the Cancer Research Institute, a New York City–based philanthropy started in 1953 by Coley's daughter. In recent decades, as molecular biology has enhanced researchers' understanding of the immune system, how it works and when it fails, cancer investigators have restocked their arsenal with more potent immunological weapons.

Among the most attractive targets for those weapons have been cancers of the circulatory and lymphatic systems, such as leukemia and lymphoma. These diseases occur when various kinds of progenitor cells called stem cells, which normally give rise to red and white blood cells (among other tissues), instead mutate and grow uncontrollably, crowding out healthy cells and robbing the body of their vital functions. Many of these so-called liquid tumors form when something goes wrong with a part of the immune system called B cells. Normally B cells generate antibodies against bacteria and viruses. (B cells also help to coordinate various other immune responses, along with another group of cells called T cells.) But when B cells become cancerous, they destroy the body from the inside out.

In the late 20th century investigators developed the biological equivalent of a guided missile that attached itself to a B cell protein (CD20) found on the surface of these cells at a specific, late stage of their existence. Dubbed rituximab, this so-called monoclonal antibody signaled the T cells to do something they do not usually do: attack and destroy these older, CD20-bearing B cells.

MICHELLE BOYER learned in 2013 that she had advanced skin cancer. After six courses of immunotherapy, she is still not cured but is living longer than her doctors initially thought possible.

Photograph by Annie Marie Musselman

The problem was that CD20 is not a cancer-specific marker. It appears on normal B cells as well as dangerous ones. So the drug killed both healthy and cancerous B cells. It turns out, however, that most people can live without B cells. (The same is not true of T cells, as the death of millions of people infected with the T cell–targeting AIDS virus tragically demonstrates.) And after the drug wore off, most patients eventually started making B cells on their own again from the stockpile of stem cells in their bone marrow. Clinical trials in the 1990s demonstrated that the combination of chemotherapy and rituximab was particularly effective against B cell–based cancers.

Koehler's leukemia originated with mutated B cells, but rituximab made her very sick and seemed only partially effective, so she stopped taking it. In addition, tests indicated her cancer would resist standard chemotherapy. Because her malignancy was rapidly getting worse, her doctors suggested an experimental immune treatment custom-designed to fight her form of leukemia. She agreed.

The goal of the new treatment was to destroy all of Koehler's B cells, as rituximab would, but with two key differences. A different protein (CD19) on the B cells was the objective. And rather than using an added drug to paint a target on that protein for T cells that were already in Koehler's body, doctors took a more direct approach. They removed some of her T cells and genetically engineered them to attack CD19 automatically, without any prompting.

Investigators call these turbocharged cells chimeric antigen receptor T cells, or CAR-T. They display some of the characteristics of both T cells and B cells in much the same way that ancient mythological creatures called chimeras were supposed to be made up of different animals. CAR-T therapy is still experimental, but the Food and Drug Administration is expected to consider approving the treatment for general use sometime next year.

The CD19-targeting CAR-T cells multiplied so quickly inside Koehler's body that the single bag of modified cells that she received on February 10, 2015, knocked out all her B cells. Unlike other patients, however, her body seems to have forgotten how to make healthy B cells. Fortunately, there is a work-around: every month she gets an hours-long infusion of artificial antibodies, called gamma globulin, to help protect her against infection. The infusions are a time-consuming hassle, she says, but "it's not chemo, so I'll take it."

CAR-T therapy did hit Koehler with something that can be worse than chemo's nausea—a storm called cytokine release syndrome. This reaction occurs when many more T cells than usual are activated at once—triggering a flood of

A VACCINE FOR CANCER?

Targeting cancer cells using their own DNA could help eliminate tumors and prevent recurrences

By Beatriz M. Carreno and Elaine R. Mardis

For more than a decade researchers have been trying to supercharge human defense systems against cancer with the help of a vaccine. These injections are not designed to prevent cancer from starting. Instead they provide patients' immune system with intel on what the enemy—cancer cells—looks like. Ordinarily, cancerous cells do not look different enough from normal cells to trigger an immune system response, but we have figured out ways to highlight and target some of the proteins that are unique to these malignancies.

Beatriz M. Carreno is an associate professor of medicine at Washington University in St. Louis. **Elaine R. Mardis** is Robert E. and Louise F. Dunn Distinguished Professor of Medicine and co-director of the McDonnell Genome Institute at Washington University in St. Louis.

Both Carreno and Mardis study how human immunology and cancer genomics may improve therapies directed at cancer.

Human cells are covered in so-called self-proteins that serve as identifying markers for the immune system. Like an ID card, they let the body know whether a substance belongs in the body and should not be attacked. Unfortunately, those proteins also dot the exterior of cancerous cells. Earlier cancer vaccine efforts, by our team and others, may have failed because they primed the immune system to look for proteins present—though at different levels—on both.

Recently, however, our team has managed to home in on proteins that are unique to the malignancies by scouring genome sequences of a patient's normal tissue and a tumor to identify proteins exclusive to the cancer. Then we study which cancer-specific proteins spark a strong response from immune molecules charged with directing the body's response to foreign substances, called major histocompatibility complex proteins, or MHCs. Using that information, we can create personalized vaccines that include MHC-containing dendritic cells from the patient that will grab the cancer proteins and present them to the immune system. That stimulus helps to generate antitumor T cell responses and marks cancer cells bearing those specific proteins for destruction.

Last year we tried this approach with three melanoma patients. As we wrote in *Science,* we found seven cancer-specific proteins that would bind to each patient's MHC molecules. We were thrilled to see a response in all three subjects: three of the seven proteins were recognized by the patients' T cells, and those T cells attacked the patients' cancer cells.

A year later the patients' immune system continued producing antitumor T cells in the blood, suggesting that our vaccines could fight off tumor recurrences. (Two of our patients' tumors shrunk or stabilized, but because they received other therapies, too, we do not know what helped.) To date, all three patients are alive and stable and show no negative side effects from the vaccine.

Our work is still in its early days. We first selected melanoma to treat because it is a cancer with many mutations and protein targets, but we plan to test this approach with other cancers, too. Before our method could become part of routine cancer therapy, we would need to study how it affects tumors long term and speed up our vaccine production time. Eventually we would like to use these vaccines to complement other cancer immunotherapies. Ultimately, we hope, vaccines will give patients a better shot against cancer.

KAREN KOEHLER remains free of cancer a year after receiving an infusion of her own immune cells, which had been genetically engineered to eradicate her leukemia.

chemical signals, called cytokines, that the immune system uses to communicate. The result can be a life-threatening frenzy of activity, in which immune cells destroy healthy tissues, causing multiorgan failure.

For Koehler, the storm came on hard and fast. She felt terrible within an hour of receiving her own altered T cells. By that night she was in intensive care where she remained for eight days—half of that time she was in a coma and totally unresponsive. She has no memory of what transpired then but can recall the hallucinations of a few days later, when she asked nurses for help packing lunch for a pair of famous golfers. Koehler has been addicted to golf since 1999, when she took it up as a way to meet men, including the man who later became her husband.

By the time Koehler got out of the hospital in early March 2015, she was incredibly weak but rebounding fast. A bone marrow test showed no evidence of cancer, and three weeks after that she was back on the golf course with her husband. The cytokine storm was terrible, but unlike chemo, the effects subsided within a few weeks and did not cause her to lose her hair. Fortunately, given that cytokine storms are fairly common with CAR-T cell treatments, physicians have begun to learn just how far to push patients like Koehler to get the greatest benefit without risking their lives.

CAR-T cell therapy must be custom-designed and produced for each patient. Manufacturing them for all the leukemia and lymphoma patients who might want them will be a challenge, as well as extraordinarily expensive—although it is too soon to know exactly how much CAR-Ts will cost because they have been used only in academic research so far. Robert Preti, founder of PCT, a CAR-T manufacturer, is working to improve the production process; he believes these are mainly engineering issues that will be solved with a few more years of hard work.

The other major challenge facing CAR-T treatment is translating its success from liquid cancers to solid tumors—the kind that forms lumps in the breast, prostate, lung, skin and other tissues. One stumbling block is that CAR-T cells have a hard time leaving the bloodstream to find a solid tumor, explains Ira Mellman, who is vice president of cancer immunology at Genentech. In the blood, the liquid tumor cells are relatively easy to locate. Even more crucial, whereas CAR-Ts can eliminate B cells in blood and lymph cancers, there is no comparable cell in solid tumors that patients can live without.

SOLID STATE

SOLID TUMORS pose other difficulties for immune treatments. They are often surrounded by a matrix of connective and other tissues, which blocks cells from entering the malignant mass. In addition, the internal pressure of a solid tumor is typically higher than its surroundings, which tends to flush out the chemical signals that the immune system uses to flag aberrant cells—not to mention many drugs.

Yet these tumors have shown some vulnerability. In 2011 the FDA approved a monoclonal antibody called ipilimumab to treat advanced cases of melanoma. Unlike traditional therapy, ipilimumab is not designed to kill tumors directly; rather it releases the biological brakes that some cancers are able to clamp on the immune system, freeing the body's defenses to do a better job.

Melanoma has a nasty habit of defrauding immune system cells. The clumps of cancer cells have an assortment of malformed proteins on the surface, which T cells are supposed to spot, swarm around and destroy before the aberrant growth has a chance to get any bigger. But every now and then a nascent tumor develops a way to send out chemical signals that tell the T cells that all is well and to stand down their attack.

In effect, the cancer cells have hijacked a normal feature of the immune system: a safety mechanism that tamps down the body's rampaging defense cells before they start damaging

Photograph by Amy Eckert

THREE IMMUNE STRATEGIES

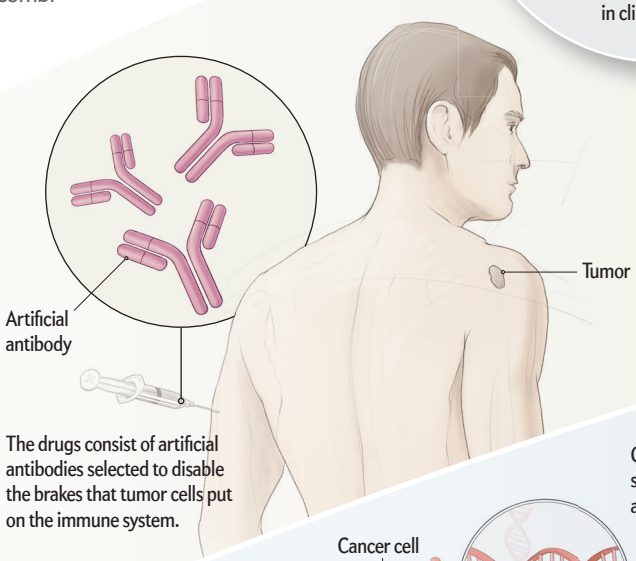
Surgery, radiation and chemotherapy have long served as the standard treatments against cancer. But clinical trials over the past five years have shown that supercharging the body's immune cells—which evolved to fight harmful bacteria and viruses, among other things—offers a powerful new addition to the mix by helping the cells to find and destroy tumors. The approaches shown here are being tested alone or in combination with other treatments.

How is immunotherapy changing the treatment of solid tumors?

Cancers of the skin, lungs and other tissues are called solid tumors because they form a mass that creates its own protective environment. Checkpoint inhibitors help to disrupt this environment, eliminating advanced skin tumors for one in five patients in clinical trials.

Checkpoint Inhibitors

Left unchecked, immune responses can be so powerful that they will destroy healthy tissue. Thus, specialized immune cells called T cells must pass several biological checkpoints before achieving full strength. Cancer cells often act on these checkpoints in a way that prevents the immune system from attacking the tumor. New drugs—called checkpoint inhibitors—disable the cancer cells' immune-dampening signals, allowing the immune system to do its job.

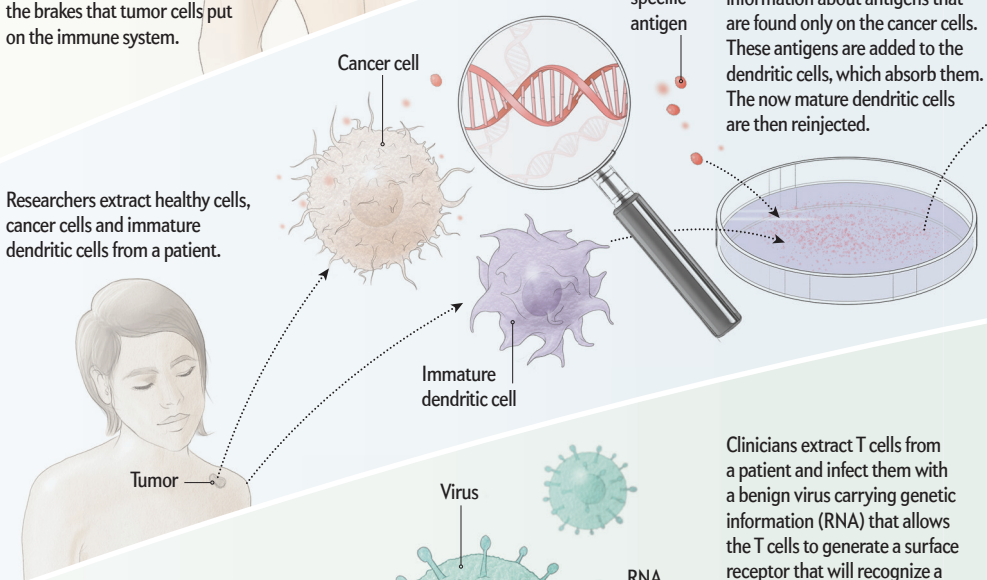


Many cancer cells hide from the immune system by displaying specific proteins that tell nearby T cells not to advance to the next stage of activation and, essentially, to leave the tumor alone.

The drugs consist of artificial antibodies selected to disable the brakes that tumor cells put on the immune system.

Dendritic Cell Vaccine

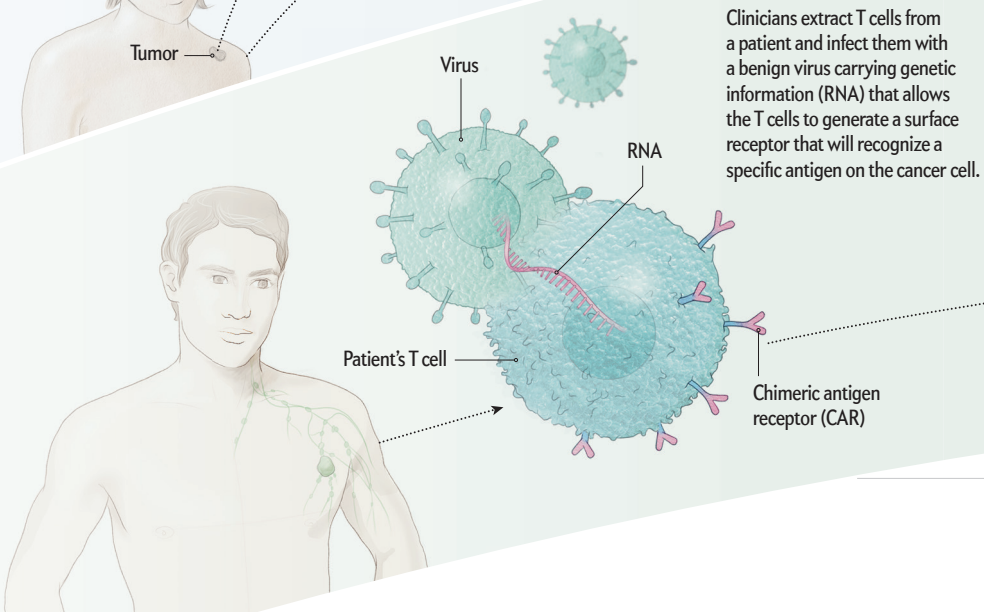
Dendritic cells normally patrol the body looking for bits of proteins called antigens that look unfamiliar. They present the offending antigens to other immune defenders, known as CD4+ and CD8+ T cells. The T cells then attack any other cells that bear the targeted antigen. By choosing antigens found on cancer cells but not on healthy ones and mixing the antigens with a patient's own dendritic cells outside the body, researchers create a kind of vaccine that will seek out and destroy those same cancer cells for years to come.



Researchers compare the genetic blueprints of malignant and healthy cells, looking for information about antigens that are found only on the cancer cells. These antigens are added to the dendritic cells, which absorb them. The now mature dendritic cells are then reinjected.

CAR-T Cells

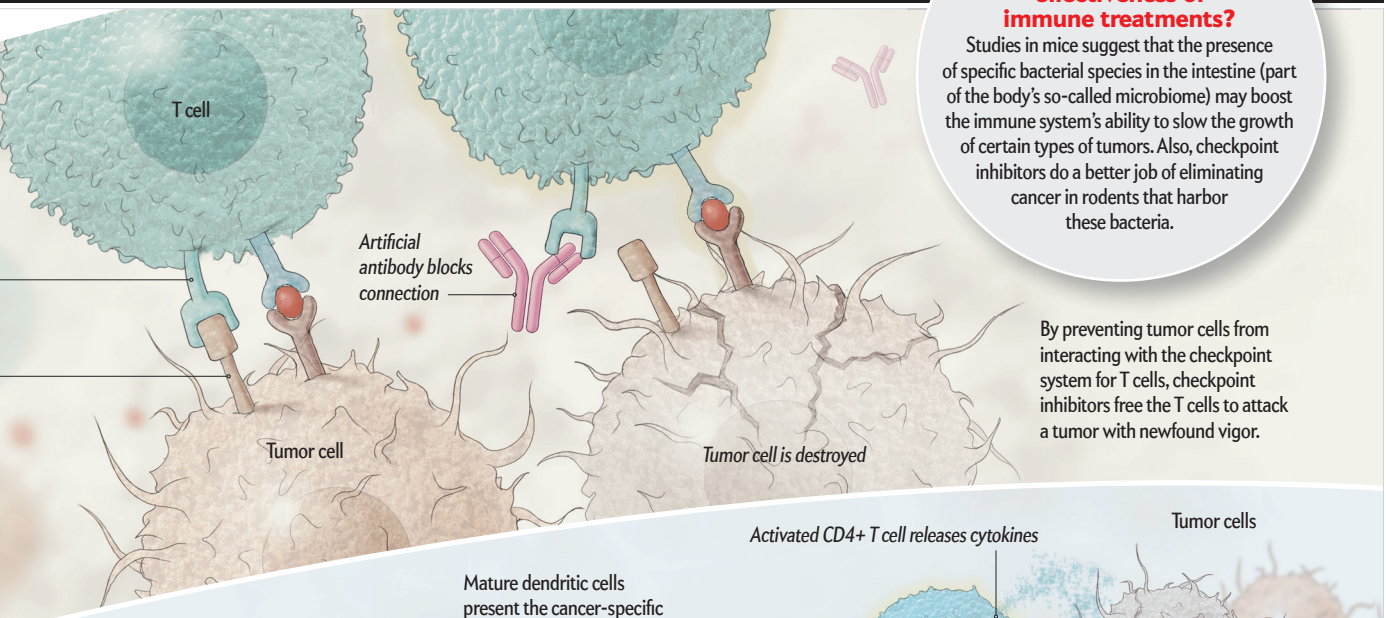
Chimeric antigen receptor (CAR) T cells combine attributes of two types of immune defenders: T cells and B cells. Molecules called receptors found on a CAR-T cell look like a hybrid of receptors on B cells and T cells. The CAR protein allows this unusual cell to both latch onto select antigens and destroy any cells that bear the target antigen. This mishmash eliminates intermediate steps typically taken by B and T cells, making CAR-T cells virtually unstoppable.



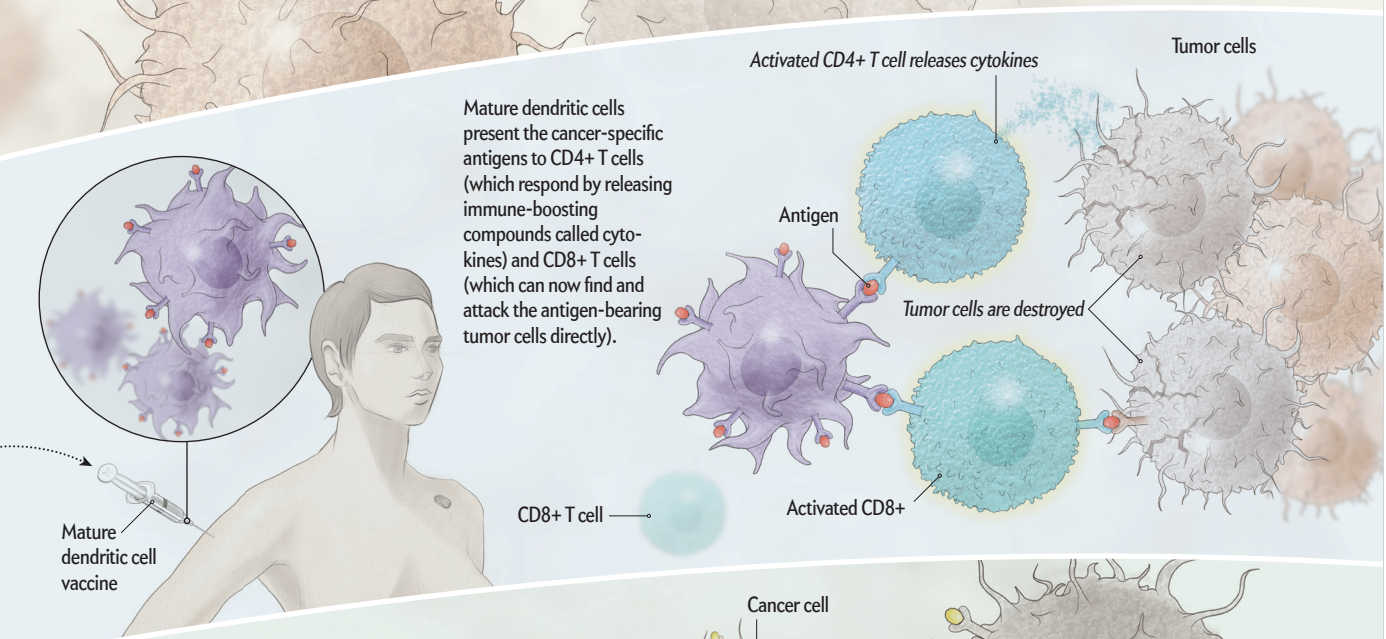
Clinicians extract T cells from a patient and infect them with a benign virus carrying genetic information (RNA) that allows the T cells to generate a surface receptor that will recognize a specific antigen on the cancer cell.

Could intestinal bacteria boost the effectiveness of immune treatments?

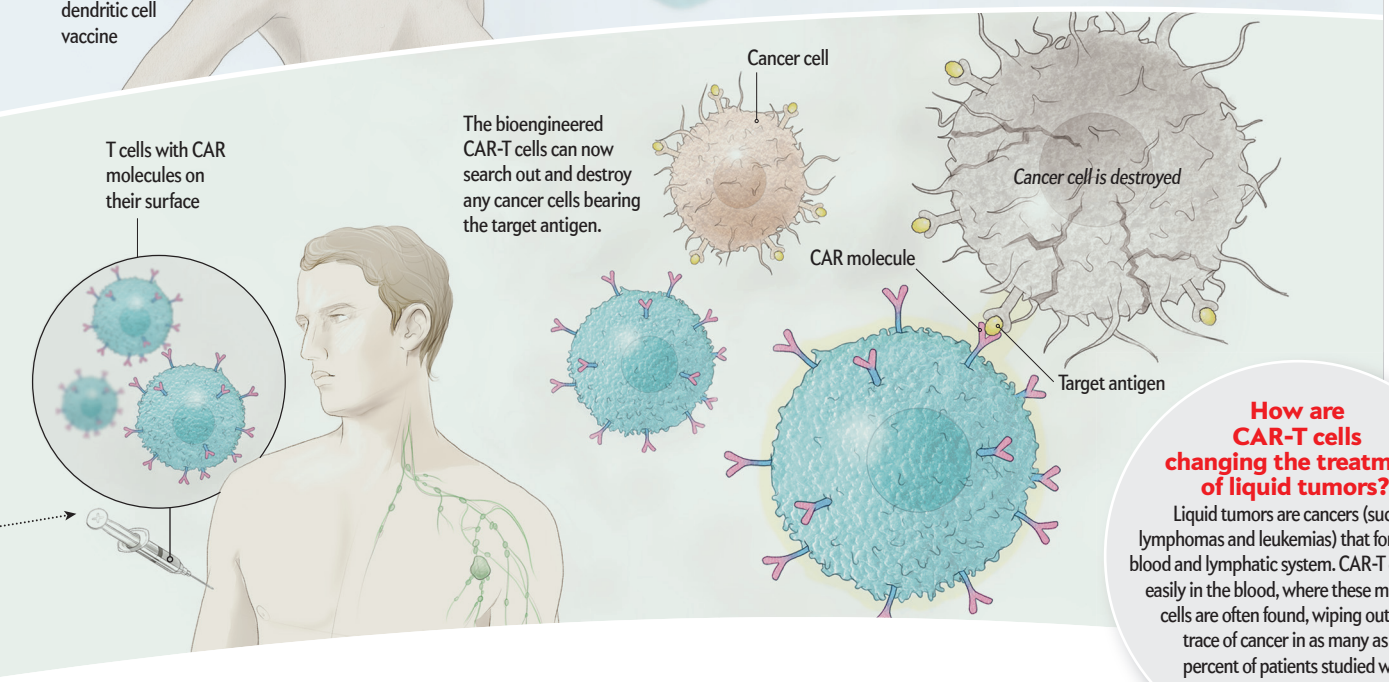
Studies in mice suggest that the presence of specific bacterial species in the intestine (part of the body's so-called microbiome) may boost the immune system's ability to slow the growth of certain types of tumors. Also, checkpoint inhibitors do a better job of eliminating cancer in rodents that harbor these bacteria.



By preventing tumor cells from interacting with the checkpoint system for T cells, checkpoint inhibitors free the T cells to attack a tumor with newfound vigor.



Mature dendritic cells present the cancer-specific antigens to CD4+ T cells (which respond by releasing immune-boosting compounds called cytokines) and CD8+ T cells (which can now find and attack the antigen-bearing tumor cells directly).



The bioengineered CAR-T cells can now search out and destroy any cancer cells bearing the target antigen.

How are CAR-T cells changing the treatment of liquid tumors?

Liquid tumors are cancers (such as lymphomas and leukemias) that form in the blood and lymphatic system. CAR-T cells travel easily in the blood, where these malignant cells are often found, wiping out every trace of cancer in as many as 90 percent of patients studied with an aggressive leukemia.

Illustration by Shizuka N. Aoki

healthy tissue. More specifically, this safety mechanism consists of a series of checkpoints, or gateways, that either rally defense cells to attack or turn them off, depending on which chemical signals are present. (If the checkpoints ever got stuck in the "open" position, the ensuing immune reaction would likely kill a person faster than any malignant growth could.) By producing proteins that block the checkpoint system, cancer cells prevent the immune system from ever ramping up to fight off cancer. Blocking that false signal with ipilimumab or other so-called checkpoint inhibitors reawakens the immune cells, allowing them once again to zero in on their targets.

Ipilimumab soon proved effective in lung cancer as well as melanoma, and pharmaceutical companies began developing other drugs that used the same strategy. Former U.S. president Jimmy Carter, 91, whose melanoma had spread to his brain, took one such drug, pembrolizumab, and he announced late in 2015 that the drug had cleared all his tumors.

Boyer, on a similar regimen with a similar disease, has not fared as well. And that is a puzzle. Some researchers speculate that Carter's advanced age may have helped him. Older cancer cells have more mutations, so his immune system may have needed just a single nudge to release the T cells that were already there. In some patients, in contrast, the T cells may never have made it into the tumor, and so there was nothing there to unblock. In other patients, the T cells seem to be in the right place, but the drug still does not work—perhaps because multiple steps need to be unjammed. A 2015 study in the *New England Journal of Medicine* showed that more melanoma patients did better when given two checkpoint inhibitors instead of one.

Still, doctors are not good at predicting who will respond to which checkpoint inhibitor or combination of treatments, and so Boyer and patients like her have to keep experimenting with different therapies. Today just more than 20 percent of advanced melanoma patients in clinical trials get a complete response from checkpoint inhibitors, with slightly more than half having some response. To confuse matters even more, some tumors that appear to attract few T cells still respond to checkpoint inhibitors, whereas the drugs sometimes have no effect on other tumors that contain lots of T cells—suggesting the cancer is playing other tricks.

That has made picking an effective solid tumor treatment

GERM WARFARE

Some types of intestinal bacteria may boost the body's ability to fight malignancy

By Maria-Luisa Alegre and Thomas F. Gajewski

Why do some patients respond well to the new cancer immunotherapies and others don't? The genetic components of the tumors or of the patients may contribute. Our work and that of other scientists now also suggest a role for differences in the makeup of the individuals' microbiome, the friendly bacteria that inhabit various parts of the body.

These bacterial communities, particularly the ones found in the intestines, can differ in their constituent species. Those species, in turn, influence the strength of a host immune system's inflammatory response by mechanisms that are still incompletely understood. Some bacteria prompt an inflammatory overreaction that nudges normal cells into becoming cancerous or mistakenly trains immune cells to attack healthy tissue in the joints, as in rheumatoid arthritis.

Sometimes bacteria might be able to trigger a therapeutic response. Our group, based at the University of Chicago, studied genetically identical strains of mice that had different microbiomes because they were raised in different environments. After the mice were injected with cells from melanoma skin cancer, the resulting tumors grew slowly in one group and faster in the other. The mice that showed slower tumor growth also mounted a stronger immune response against their tumor. Strikingly, transplanting the microbiome from mice with slower-growing tumors into the other mice—we do this by transferring fecal material between the animals—resulted in slower-growing tumors in the latter group.

By analyzing the DNA in stool samples from the two mouse groups, our team found two bacterial species from the genus *Bifidobacterium* that seemed responsible for improved antitumor activity. Remarkably, feeding the mice just one strain—either *Bifidobacterium longum* or *Bifidobacterium breve*—was sufficient to boost the immune system and slow down tumor growth in recipient mice. The presence of these beneficial bacterial strains even determined how well one new immunotherapy drug, a so-called checkpoint inhibitor [*see main text*], worked. The tumors disappeared entirely in mice that were treated with the checkpoint inhibitor and whose microbiome included the *Bifidobacterium* species; mice lacking *Bifidobacterium,* however, experienced only a partial response to the drug but were cured if also fed the right bacterial strains.

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A second team of researchers—based primarily in France—conducted a similar experiment with a different checkpoint inhibitor. They determined that another bacterial genus, *Bacteroides,* allowed the treated animals to eliminate injected tumors. Giving the animals an antibiotic that killed these microbes rendered the anticancer drug ineffective—something that should give doctors pause, given how many cancer patients also receive antibiotics. Results from the French and Chicago groups were published in November 2015 in *Science.*

Obviously we need to categorize the bacteria in the human microbiome and their potential antitumor effects more completely before we can recommend any treatments in people. Whereas bacteria such as *Bifidobacterium* seem to have favorable effects, other strains might allow tumors to grow more rapidly. (Consuming yogurt to boost immune treatments might not work either. Yogurt typically contains *Bifidobacterium lactis* or *Bifidobacterium bifidum,* which may not have the same effects as the species used in the recent mouse studies.) Nor would clinicians want to boost the immune system too much, lest they trigger autoimmune diseases.

for a particular individual a matter of trial and error, as Boyer's experience illustrates. Two years after surgery to remove the cancerous mole from her back, she learned that the melanoma had returned and was spreading throughout her lungs and chest. Because the growths were now too large to be cut out, Boyer agreed with her physicians to take part in a clinical trial at the beginning of 2013 that would inject her with high doses of interleukin-2 (IL-2), one of dozens of different chemical signals that help to boost the immune system's ability to fight cancer. At first the drug seemed to stop the growth of Boyer's tumors, but after three months, scans showed that the cancer was on the move again.

Boyer opted for a second clinical trial, this time pairing the recently approved checkpoint inhibitor ipilimumab with still another immune-signaling molecule known as IL-21. Within a few weeks, however, the side effects of the IL-21 treatment (nausea, diarrhea and unbearable pain) had become so disabling that Boyer had to stop getting the injections, although she continued receiving the ipilimumab. By the end of 2013 some of the cancerous spots had started to expand, and so her medical team opted for radiation to try to limit the growth. By spring of the following year a few of these tumors were smaller, but new ones had appeared on her head and in her breast.

Surgery dispatched the lump in her breast, and two other immune-boosting therapies seemed to hold the rest of her tumors in check for a while. By January 2015, however, it became clear that she needed another plan of action—new spots had begun to grow in her brain, breast and abdomen. A month later she entered a clinical trial, which combined yet another checkpoint inhibitor with a drug that is supposed to slow tumor growth. As this article went to press, Boyer's cancerous spots remain stable, and some of them have even shrunk a little.

There is no denying that so many treatments have battered Boyer's body. She spends her nights and many of her days in a plush loveseat to rest her back. She goes to work as a structural engineer most mornings on the weeks she has off from her sixth and current round of treatment. Otherwise she entertains herself by playing video games—Call of Duty is her favorite. All told, however, she does not regret trying six different immunotherapy regimens so far. "It seems to me that some of these treatments maybe slowed down the growth a little bit," she says. One of her doctors, Boyer remembers, "said part of the game for melanoma was not necessarily finding the right treatment now, but keeping yourself alive long enough until they find the right treatment." And so she is and so far accepts her current quality of life.

LOOKING AHEAD

BECAUSE BOYER and other patients are living long enough to feel some contentment, Genentech's Mellman is excited. For immunotherapy, possibilities have begun to turn into actual results in patients, he says. Investigators no longer worry about whether their research will eventually help someone; now they can spend their time making effective treatments better. "We need to find the boundaries and limitations and figure out how to get around them," Mellman says, but "this is an incredibly inspiring and thrilling way to do science."

Eventually the process of selecting an immune treatment will become more logical, he believes. A patient with a solid tumor might first have the tumor biopsied to look for the presence of T cells. If enough T cells were in the tumor, the person would likely be given a single checkpoint inhibitor or maybe several inhibitors. (At present, the FDA has approved three checkpoint inhibitors, but more than a dozen others are under development.) If the tumor has not already attracted many T cells, doctors may try various other techniques to both drive the immune cells in and call the immune system's attention to the abnormal growth before opening the checkpoints.

Researchers are also considering how to use standard cancer care, including radiation and chemotherapy, to boost the immune response. Killing a number of tumor cells with lower doses of chemotherapy or radiation should release lots of cellular debris from the tumor, thereby alerting the immune system to send T cells to whatever abnormal growth remains. (Getting the balance right may be tricky because too much chemotherapy and radiation have also been shown to suppress parts of the immune system.) Then, the addition of a checkpoint inhibitor might be able to effectively fight the weakened cancer before it has a chance to recover. But scientists have only just begun to test such hypotheses.

Finally, as more and more immunotherapies are approved by the FDA, they present an entirely different, nonmedical challenge: price. Combining therapies raises the cost of what are already quite expensive treatments. The global market for oncology drugs is now approaching $100 billion a year, according to IMS Health, a medical data company, but drug firm executives acknowledge that insurers and the public will not be willing or able to indefinitely combine drugs that can run $150,000 or more per patient. They are looking at manufacturing improvements, lower doses and shorter treatment times, among other approaches, to lower the eventual cost of treatment.

Even today's curative therapies are far from perfect. Koehler still has some lingering effects from her treatment. She tires more easily than she used to. If she goes to lunch with friends, she might not have the energy to take a hike later with her husband. "The toughest part now is how far do I push myself," she says. But Koehler is able to enjoy the retirement she took when her first therapy did not work. She golfs, hikes or snowshoes when the weather permits. Inspired by the therapy dogs that visited her during her hospital stay, she brings her own golden retriever, CJ, to the local high school to help relieve exam stress among students there. Cancer doctors believe immunotherapy will soon allow them to give many more patients similar opportunities to enjoy a new lease on life. SA

MORE TO EXPLORE

The Basic Principles of Chimeric Antigen Receptor Design. Michel Sadelain et al. in *Cancer Discovery*, Vol. 3, No. 4, pages 388–398; April 2013. http://cancerdiscovery.aacrjournals.org/content/3/4/388.full.pdf

2015 Guidance on Cancer Immunotherapy Development in Early-Phase Clinical Studies. Guidance Development Review Committee et al. in *Cancer Science*, Vol. 106, No. 12, pages 1761–1771; December 2015. http://onlinelibrary.wiley.com/doi/10.1111/cas.12819/epdf

Advances in Immunotherapy for Melanoma. Jason M. Redman et al. in *BMC Medicine*, Vol. 14, Article No. 20; February 6, 2016. http://bmcmedicine.biomedcentral.com/articles/10.1186/s12916-016-0571-0

FROM OUR ARCHIVES

Cancer's Off Switch. Jedd D. Wolchok; May 2014.

The problem was that CD20 is not a cancer-specific marker. It appears on normal B cells as well as dangerous ones. So the drug killed both healthy and cancerous B cells. It turns out, however, that most people can live without B cells. (The same is not true of T cells, as the death of millions of people infected with the T cell–targeting AIDS virus tragically demonstrates.) And after the drug wore off, most patients eventually started making B cells on their own again from the stockpile of stem cells in their bone marrow. Clinical trials in the 1990s demonstrated that the combination of chemotherapy and rituximab was particularly effective against B cell–based cancers.

Koehler's leukemia originated with mutated B cells, but rituximab made her very sick and seemed only partially effective, so she stopped taking it. In addition, tests indicated her cancer would resist standard chemotherapy. Because her malignancy was rapidly getting worse, her doctors suggested an experimental immune treatment custom-designed to fight her form of leukemia. She agreed.

The goal of the new treatment was to destroy all of Koehler's B cells, as rituximab would, but with two key differences. A different protein (CD19) on the B cells was the objective. And rather than using an added drug to paint a target on that protein for T cells that were already in Koehler's body, doctors took a more direct approach. They removed some of her T cells and genetically engineered them to attack CD19 automatically, without any prompting.

Investigators call these turbocharged cells chimeric antigen receptor T cells, or CAR-T. They display some of the characteristics of both T cells and B cells in much the same way that ancient mythological creatures called chimeras were supposed to be made up of different animals. CAR-T therapy is still experimental, but the Food and Drug Administration is expected to consider approving the treatment for general use sometime next year.

The CD19-targeting CAR-T cells multiplied so quickly inside Koehler's body that the single bag of modified cells that she received on February 10, 2015, knocked out all her B cells. Unlike other patients, however, her body seems to have forgotten how to make healthy B cells. Fortunately, there is a work-around: every month she gets an hours-long infusion of artificial antibodies, called gamma globulin, to help protect her against infection. The infusions are a time-consuming hassle, she says, but "it's not chemo, so I'll take it."

CAR-T therapy did hit Koehler with something that can be worse than chemo's nausea—a storm called cytokine release syndrome. This reaction occurs when many more T cells than usual are activated at once—triggering a flood of

A VACCINE FOR CANCER?

Targeting cancer cells using their own DNA could help eliminate tumors and prevent recurrences

By Beatriz M. Carreno and Elaine R. Mardis

For more than a decade researchers have been trying to supercharge human defense systems against cancer with the help of a vaccine. These injections are not designed to prevent cancer from starting. Instead they provide patients' immune system with intel on what the enemy—cancer cells—looks like. Ordinarily, cancerous cells do not look different enough from normal cells to trigger an immune system response, but we have figured out ways to highlight and target some of the proteins that are unique to these malignancies.

Beatriz M. Carreno is an associate professor of medicine at Washington University in St. Louis. **Elaine R. Mardis** is Robert E. and Louise F. Dunn Distinguished Professor of Medicine and co-director of the McDonnell Genome Institute at Washington University in St. Louis.

Both Carreno and Mardis study how human immunology and cancer genomics may improve therapies directed at cancer.

Human cells are covered in so-called self-proteins that serve as identifying markers for the immune system. Like an ID card, they let the body know whether a substance belongs in the body and should not be attacked. Unfortunately, those proteins also dot the exterior of cancerous cells. Earlier cancer vaccine efforts, by our team and others, may have failed because they primed the immune system to look for proteins present—though at different levels—on both.

Recently, however, our team has managed to home in on proteins that are unique to the malignancies by scouring genome sequences of a patient's normal tissue and a tumor to identify proteins exclusive to the cancer. Then we study which cancer-specific proteins spark a strong response from immune molecules charged with directing the body's response to foreign substances, called major histocompatibility complex proteins, or MHCs. Using that information, we can create personalized vaccines that include MHC-containing dendritic cells from the patient that will grab the cancer proteins and present them to the immune system. That stimulus helps to generate antitumor T cell responses and marks cancer cells bearing those specific proteins for destruction.

Last year we tried this approach with three melanoma patients. As we wrote in *Science,* we found seven cancer-specific proteins that would bind to each patient's MHC molecules. We were thrilled to see a response in all three subjects: three of the seven proteins were recognized by the patients' T cells, and those T cells attacked the patients' cancer cells.

A year later the patients' immune system continued producing antitumor T cells in the blood, suggesting that our vaccines could fight off tumor recurrences. (Two of our patients' tumors shrunk or stabilized, but because they received other therapies, too, we do not know what helped.) To date, all three patients are alive and stable and show no negative side effects from the vaccine.

Our work is still in its early days. We first selected melanoma to treat because it is a cancer with many mutations and protein targets, but we plan to test this approach with other cancers, too. Before our method could become part of routine cancer therapy, we would need to study how it affects tumors long term and speed up our vaccine production time. Eventually we would like to use these vaccines to complement other cancer immunotherapies. Ultimately, we hope, vaccines will give patients a better shot against cancer.

healthy tissue. More specifically, this safety mechanism consists of a series of checkpoints, or gateways, that either rally defense cells to attack or turn them off, depending on which chemical signals are present. (If the checkpoints ever got stuck in the "open" position, the ensuing immune reaction would likely kill a person faster than any malignant growth could.) By producing proteins that block the checkpoint system, cancer cells prevent the immune system from ever ramping up to fight off cancer. Blocking that false signal with ipilimumab or other so-called checkpoint inhibitors reawakens the immune cells, allowing them once again to zero in on their targets.

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TOURISTS ARE EVERYWHERE in the Galápagos Islands, disturbing exotic species and their habitats: young sea lions (*above*), a marine iguana (*top right*) and fragile plant life on Isabela Island (*bottom right*).

ECOLOGY

GALÁPAGOS STAMPEDE

A relentless rise in visitors could ruin the famous biodiversity hotspot in only a few years *By Paul Tullis*

At the southern tip of the island of Santa Cruz in the Galápagos, a gorge known as Las Grietas is home to a species of parrot fish: a brilliantly colored creature about 18 inches in length. The pool where the fish live was created long ago, when large waves spilled over the island's raised edge and into a deep crevice. Today it is refreshed by rainwater that seeps through the porous volcanic rock that forms the steep gorge. Through it all, the small parrot fish population has been evolving in the pool, its water so clear one can see through more than 65 feet to the vertebrates lurking at the bottom.

In August 2014 I arranged to hike there with naturalist Andrés Vergara. We met at the Finch Bay Eco Hotel and walked about

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10 minutes over uneven earth and sand at an easy pace. But then we took the final stretch of the trail—up over jagged rocks, then down the gorge's stony walls in a crablike clamber to the pool's edge. This last part was hazardous enough to discourage the casual tourist; only a few adventurous individuals had actually reached the pool. It is a beautiful spot. Rock ledges up to 30 feet

above provide places from which a visitor with enough courage can leap into the water below.

We were lucky to visit when we did because Las Grietas was shortly thereafter closed for trail improvements. It reopened in December 2014. Vergara, who works as a guide for the Galápagos National Park Service, phoned me at that time and said the spot now has a boardwalk over the rocks, an elaborate staircase leading down to the water and a wood platform for the plunge into the pool. "It's part of a plan of the Galápagos National Park to make things better for the community and visitors," he said. The improvements have dramatically increased the number of visitors, which tripled between July 2014 and July 2015, when 7,109 people made the walk.

What all these humans mean for the viability of parrot fishes is unclear. Will increasing amounts of sandwich crumbs, washed-off sunscreen and the inevitable plastic wrappers pollute their unique habitat—and ultimately ruin the pool's tourist appeal?

Ever since Charles Darwin visited the islands in 1835 and observed them as a living laboratory of natural selection, the Galápagos has become known the world over as one of the best places to see wildlife. The islands hold 14 species of tanagers (known as Galápagos finches) and 12 species of tortoise. Penguins and flamingos live within a few miles of one another. Sea lions are so well fed on abundant fish that they do not even bother with the penguins, which they readily hunt in other parts of the planet. The list of wildlife attractions, promoted on slick brochures and Web sites, is why a modicum of adventurous—and wealthy—tourists have been compelled for decades to make the long journey to the archipelago.

In recent years, however, the trickle of tourists has turned into a flood. In the early 1990s, 41,000 people a year visited the Galápagos. In 2013 the figure exceeded 200,000 for the first time. More than 224,000 visitors arrived in 2015, another record. This growth is fueled in part by need. Ecuador is struggling financially. It relies on oil for 44 percent of its export revenues. To bolster its finances and make up for the recent drop in oil prices, the government has turned to tourism, allowing industry to more easily develop the islands, and has chipped in with projects such as the one at Las Grietas.

"The government is clearly working to significantly increase tourism in the Galápagos; there's no doubt about it," says Swen Lorenz, who has a background in finance and who, from 2011 until 2015, was executive director of the Charles Darwin Foundation, which advises the government on ecological issues.

It is possible to conduct tourism in a way that preserves natural areas, benefits local people, and even finances conservation of habitats and species. But this responsible "ecotourism" still has an impact on habitat, and it is no longer the only kind that is happening in the Galápagos. The influx of travelers is on a collision course with the very thing that everyone comes to see: the wildlife. Of 20 endemic species that are critically endangered, 16 live on the four inhabited islands that get the most visitors. New invasive species, brought in large part by visitors, are already taking over certain ecological niches. A green iguana, which could spread disease from the mainland to endemic species, was captured in Puerto Ayora on Santa Cruz last August; no one knows how it got there or how many others may have come with it.

The Galápagos would not be the first ecologically sensitive place to be permanently damaged by tourists. Visitors lop off corals for souvenirs in the Great Barrier Reef. Fragile Antarctica is being discovered by cruise ships. There is now a Walmart at Teotihuacán, the ancient Mesoamerican city in Mexico that was carefully exhumed and restored. Ecuador, by letting the tourism industry develop unabated, may be presiding over the destruction of a jewel of biodiversity. If that happens, the islands could also lose the interest of tourists and the income they bring.

In 2013 Ecuador took a step toward putting the Galápagos on a sustainable path. President Rafael Correa ordered a study of the impact of growing tourism on the islands. The report that came

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Map by Mapping Specialists

IN BRIEF

A steep rise in the number of tourists visiting the Galápagos Islands is threatening the very biodiversity people come to see. Ecuador has encouraged the increase to bring in revenue. But the former head of the Galápagos National Park, who was fired, and independent wildlife experts say the country must set an annual cap on visitors or the islands will be ruined.

The experts filed a report in early 2014 that recommended a cap of 242,000 people, but they say President Rafael Correa's administration has ignored it.

In the meantime, the park service is building walkways and other infrastructure to make it easy for visitors to reach ecologically sensitive spots, which could be overrun. And small, illegal hotels have expanded to bring in more tourists than ever before.

PRECEDING PAGES: ERIC KRUSZEWSKI Getty Images (sea lions); MATT MOYER Getty Images (iguana); DOUG CHEESEMAN Getty Images (tourists)

NEW BOARDWALKS and stairs, like these on the island of Bartolomé, make it easy for numerous visitors to reach pristine places, threatening the landscape and wildlife in the process.

JOEL SARTORE Getty Images

back was dire: if Ecuador did not quickly set a cap on the number of visitors each year, continuing development would imperil the archipelago's biodiversity and its attractiveness to tourists. So far, however, Correa's administration has not heeded this warning.

CONTROVERSIAL CAP ON TOURISTS

THE MOVE TO ASSESS tourism's impact began in the late summer of 2013, when Arturo Izurieta received a surprise phone call from Lorena Tapia, at the time Ecuador's minister of the environment. Izurieta, a native of Ecuador who had lived more than 25 years in the Galápagos, was working as a conservationist in Australia. Tapia was offering him a chance to return home to the archipelago and a position he held there in the early 1990s: director of the Galápagos National Park and Marine Reserve.

What is more, Tapia wanted Izurieta to take on the problem of sustainable development, according to Izurieta. (Tapia, through a spokesperson, declined a request to be interviewed by SCIENTIFIC AMERICAN.) President Correa, she told him, had just requested a study of how many tourists the Galápagos could accommodate. How many sites could be safely opened? What was the general impact of human presence on the islands? The latter "was a very exciting question," Izurieta recalls. "She asked me, 'How are we going to figure this out?'" Correa wanted an answer within a year.

Izurieta got started in September. He quickly assembled a commission of experts, such as Stephen J. Walsh, a geographer who directs the Center for Galápagos Studies at the University of North Carolina at Chapel Hill, and Carlos Mena, who, with Walsh, co-directs the Galápagos Science Center, which is jointly run by U.N.C. Chapel Hill and Ecuador's University of San Francisco, Quito. His panel included biologists, geographers and a business school professor.

The team decided to define scenarios of tourism growth and let the government decide which scenario it wanted to pursue based on its goal, be that revenue generation or conservation of the islands, or some balance between the two. "The scenario you choose is based on the amount of risk you're willing to assume," Walsh says, and on what the government values. If the government decided to double the number of tourists, for example, it had to accept greater risk that habitat would be trodden and that more diesel spills and pollution from incoming ships would occur. "Every time a decision about the human dimension is made, it affects what the Galápagos will look like in the future," Walsh explains.

Walsh and Mena developed mathematical models of the islands' ecosystems to determine how different levels of growth, for different categories of tourist, would affect various aspects of the environment. The 19 islands, and their roughly 145 protected sites, experience different impacts depending on whether a tourist is staying on land or on a boat anchored along the shore, for example. Even a visitor's nationality matters: waste production, for example, grows more quickly as the percentage of tourists from the U.S. rises. The team incorporated decades' worth of data and fed them into algorithms to plot how changes to any one factor affected the others.

As Walsh and Mena raised the number of annual visitors, the models revealed critical thresholds—points at which negative effects began to change the environment dramatically, sending certain species over the edge toward ruin. The models basically showed a death spiral from unchecked growth in tourism. Demand for private development to support that growth would destroy habitat, and plants and animals would go extinct. After a

decade or so, the decline in species would become so noticeable that the travel industry would diminish as a result. Tourism-funded programs to reestablish ailing species would then be left underfunded. "If we continue growing," Izurieta says, "very soon we will reach the point of no return."

How soon? Izurieta's report, commonly referred to as *Scenarios for Sustainability,* puts the date at 2017. Allowing unlimited growth would bring more revenue to Ecuador over the next 10 years than the other scenarios. But revenue from tourism would peak in 2027 and then decline. "The number of visits will fall below what we have today," Izurieta says.

The alternative stabilization scenario, which would cap visitors at 242,000 annually, would mean less revenue between now and 2027, but it would virtually guarantee ongoing revenue annually for decades beyond. The cap, Izurieta says, is based on the carrying capacity (the number of visits over a certain time period) of sites within the protected areas. It would undercut the market for giant hotels and reduce demand for small, illegal hotels as well, but it would allow the light-footprint, higher-priced ecotourism that sustained the islands for decades to continue more or less unimpeded.

CERTAIN GIANT TORTOISES have made a comeback thanks to conservation efforts funded in part by park entry fees. If managed tightly, tourism could coexist with native species.

MANFRED GOTTSCHALK *Getty Images*

Izurieta's commission filed its report in February 2014. Through most of 2014, according to Izurieta and two other conservationists I spoke with, Tapia discussed the report with the current minister of tourism, the national director of planning, the head of the Galápagos governance council and the director of the national parks. The group "had various meetings to polish the presentation that would be made to President Correa," Izurieta says. "In those meetings, there was a consensus that the stability scenario would be advised."

It was hard for the group to get national politicians to focus on environmental policy in early 2015, however. The legislators were consumed with revising the 1998 Special Law for Galápagos, which determines things like the minimum wage and the number of boat licenses. The report group decided to delay presenting Izurieta's study to President Correa until a new law was passed. That happened in June 2015.

Two months earlier, though, the environmental ministry fired Izurieta—without explanation, he says. Tapia, through a spokesperson, declined to comment. The report has been sitting on a shelf ever since, according to several sources.

ILLEGAL HOTELS, FOREIGN INVESTORS

IZURIETA FIRMLY BELIEVES that a cap on tourists is essential. The "Galápagos is the most carefully managed tourist destination in world," says Matt Kareus, executive director of the International Galápagos Tour Operators Association. "While [Izurieta] was in charge [of the park], there was no increased impact on the protected sites—none. It was extremely well managed." But any number of tourists, no matter how "eco" they are, carries risk. Simply bringing in fuel to support even low-impact travel increases spills, carbon emissions and land degradation. Ecotourists can unwittingly bring invasive species into the islands just as well as anyone else. The parasitic fly that is wiping out the mangrove finch was probably introduced in the 1960s, when tourist visits were less than one twentieth of what they are today.

"We still have time to stabilize the number of tourists, but we need to start now," Izurieta told me by phone in April 2015. "If we don't, I don't know what's going to happen to the islands." It is easy to see how the archipelago's white sand beaches, 80 degree Fahrenheit ocean water, gorgeous views, and activities such as snorkeling and sea kayaking could make the Galápagos "a holiday destination like any other, with spa hotels and streets lined with T-shirt shops," says Lorenz, former director of the Charles Darwin Foundation.

Correa's government appears to be taking no measures to slow growth, relying instead on changes to the Special Law they hope will discourage tourism. By not choosing, Ecuador's leaders are selecting unchecked growth by default. They continue to grant airlines additional flights to Seymour Airport, the archipelago's biggest, on the barren island of Baltra. They give tourists park entry licenses even when the applicants are unable to show they have a reservation at a legal hotel, as is nominally required (unlicensed hotels are everywhere). Officials grant so-called temporary resident permits with no expiration date.

Close observers say a cap on visits is not forthcoming, because Correa's advisers do not want to deliver the bad news that tourism will have to slow. "I don't think a cap is going to be established," says Juan Carlos Garcia, conservation director for the Ecuador branch of the World Wide Fund for Nature. "Everyone is afraid of giving any number."

Two changes to the revised Special Law that were passed in April could invite more trouble. One eliminated the requirement that residents of the Galápagos must own the majority of any investment in the islands; now locals must only be "involved" in new development, a vague term open to wide in-

terpretation. The second change allows park boundaries to be altered. Technically, these two changes together would make it possible for foreign investors to rush in, develop what was once parkland and leave locals with little economic gain for the ecosystem losses.

Without a cap, the number of land-based tourists is almost certain to grow, says Kareus of the International Galápagos Tour Operators Association. They use more energy and leave more waste than travelers who spend their nights on boats along the shore. The Galápagos National Park Service regulates tourist visits to sensitive areas such as the island of North Seymour, where magnificent frigate birds and blue-footed boobies nest and raise their young, and Tortuga Bay, where sea turtles bury their eggs, through its management system. But the system was designed for a ratio of boat berths to hotel beds of between 1:1 and 1:2.

Today there are about five times as many hotel beds as boat berths, a ratio of 1:5, according to official statistics cited by Izurieta, who has taken over for Lorenz as director of the Darwin foundation. And that does not count many unlicensed hotels going up, especially on Santa Cruz. A moratorium on new hotels or hotel expansion was put in place about a decade ago but was never enforced, according to Felipe Cruz, deputy executive director of the foundation, who has lived in the islands for 30 years. A house in his neighborhood recently added two stories, he says, and he was surprised to see a "hotel" sign go up when construction was completed.

Much of the construction, Cruz and others say, is for cheap facilities catering to backpacking college students and weekenders from South America. For that region's expanding middle class, a $300 flight from Santiago or Buenos Aires to Baltra is within reach of more people than ever.

Izurieta applauded the recent lifting of the hotel moratorium because he believes it will lead to new construction that is better regulated. Legalizing what was going on anyway will put these facilities under the eye of authorities. Although the Ministry of Tourism says that new hotels will be limited to 35 rooms each, it will need to resist industry pressure, Izurieta says. Lorenz sent me documents produced by a financial consultant company called Stock & Fund Managers, which promised that it and an investment group had "secured two prime locations" for development of 39 "villas" and two hotels totaling 95 rooms, with one of the developments offering "restaurants, entertainment areas, meeting rooms, spas and swimming pools."

Lorenz says that in 2014 Kempinski Hotels, headquartered in Germany, and Waldorf Astoria Hotels & Resorts presented plans to President Correa for large developments. The hoteliers said they have no confirmed projects in the islands, and Ecuador's tourism ministry declined to comment, although the ministry issued a statement on September 9, 2015, avowing that the Galápagos governance council's approval of three projects with 36 rooms between them "confirms once again that mega hotels are banned in the Galápagos."

POLITICAL WILL

CONSERVATION AND TOURISM in the Galápagos are not incompatible; revenue from visitors can help protect habitat and wildlife. I visited a nursery working to recover a species of giant tortoise that had been nearly wiped out by rats, which devour their eggs. Soon after my visit, a study in *PLOS ONE* reported that a similar captive breeding program for the giant tortoise population on the island of Española, along with goat-eradication efforts there, had been so successful that the population is now considered stable. Park entry fees financed much of this work, along with funds from environmental organizations. Wildlife conditions on the uninhabited islands, where invasive species such as goats had run rampant as well, are also improving thanks to other conservation programs financed by tourism.

Eliécer Cruz, a former Galápagos National Park Service director whom President Correa made president of the Galápagos governance council in April 2015, told me last October he was working on changes to the immigration system to limit the number of visitors. He also said he and the relevant ministers had been talking just the day before about presenting *Scenarios for Sustainability* to President Correa, at long last. He said a cap on visitors of 242,000 a year, the number that the report says is sustainable, is "really important." But in February of this year, the current head of the Galápagos National Park System, Walter Bustos, confirmed that the report still had not been presented.

Bustos told me that the new minister of environment, Daniel Ortega, has decided to "update the information" provided in Izurieta's report. When asked about this, Walsh wrote in an e-mail that the request "is not about changing the outcomes from the earlier model run" but to "look explicitly at the economics of tourism in the Galápagos."

In any case, Bustos said, "it's not so easy" to set a limit of 220,000 a year, adding that "I think we can achieve 220,000 through other policies." He pointed to new hotels being restricted to 35 rooms and requiring the approval of the Galápagos council, as examples of measures that will "slow the rate of growth" of tourism on the islands. The question is whether this can be done before crossing the 242,000 line, which will happen in the first half of 2017 at current rates.

As for why Izurieta was fired, he will not give his opinion on the record. He wrote on Facebook a few days after losing his job in April that it was "a political decision" and that "though I respect it, I do not necessarily agree with it."

In the meantime, tourism construction continues apace. A $2.5-million infrastructure project is under way. Some of the funds will go to Tagus Cove on the island of Isabela, where, on September 29, 1835, Darwin encountered "great black lizards between three and four feet long." It is not clear from his diary whether he arrived by boat or made the challenging climb down from the surrounding hills, but either way the cove is difficult to reach. The park service plans to build stairs. SA

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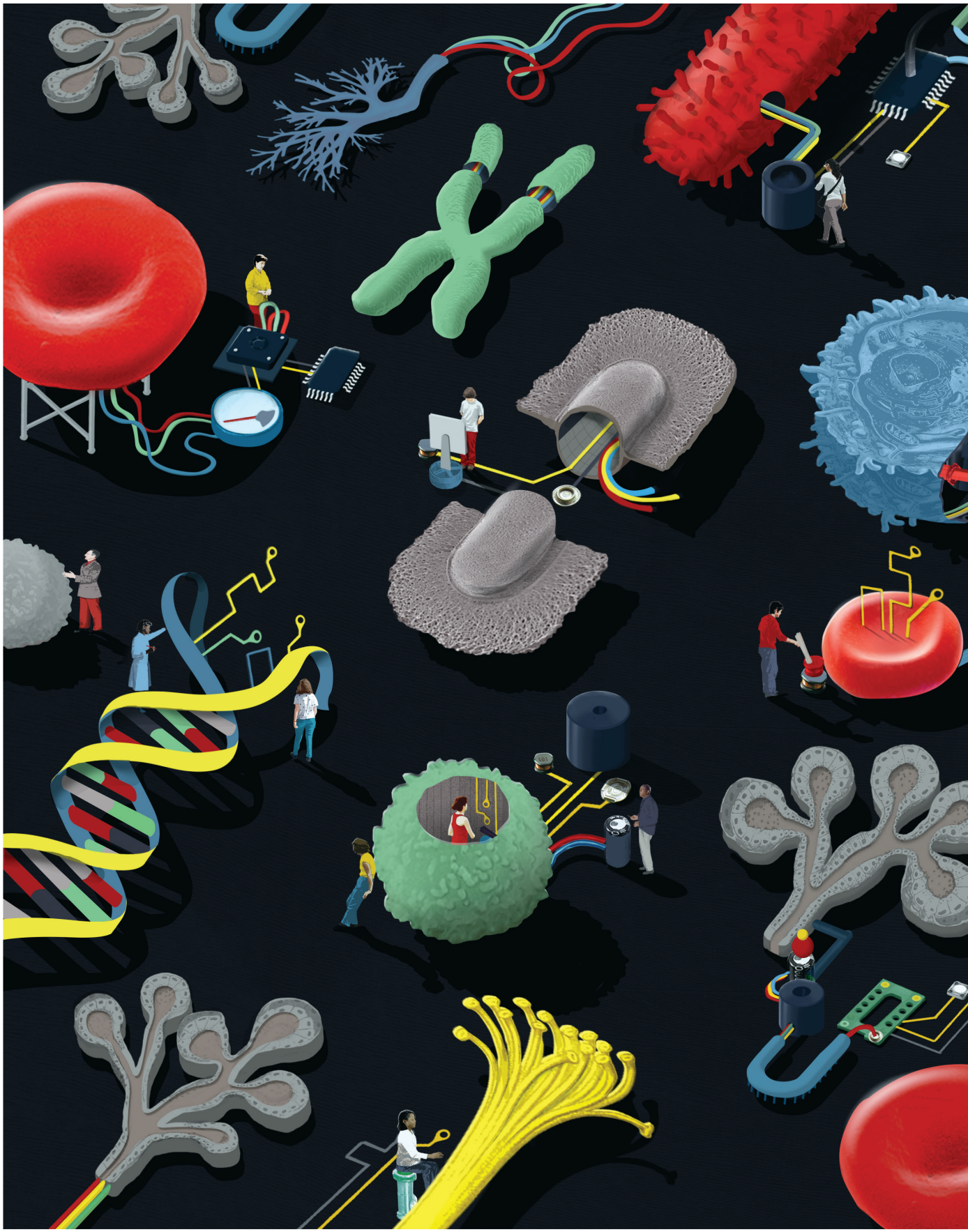
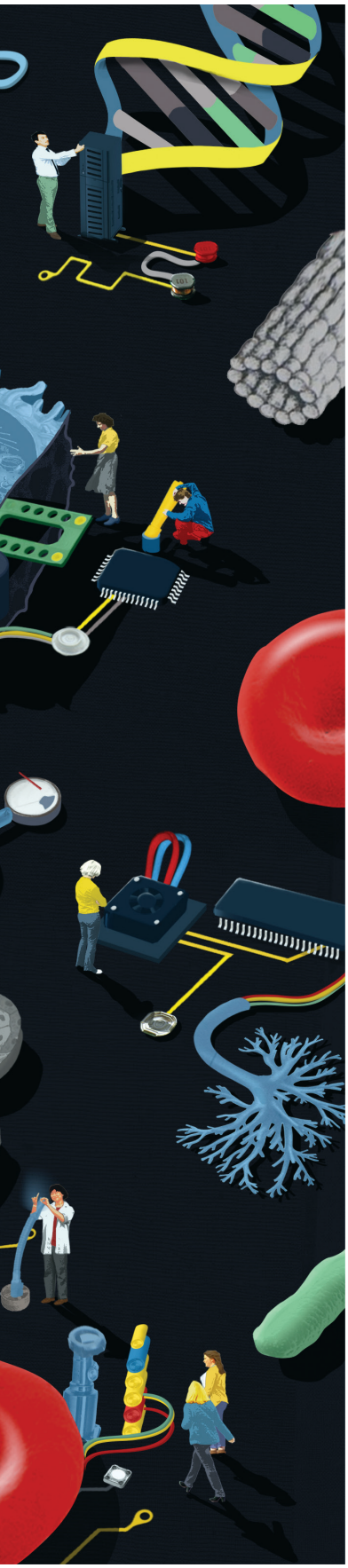




BIOENGINEERING

MACHINE LIFE

Synthetic biologists are close to putting living cells to work diagnosing human diseases and repairing environmental damage

By Timothy K. Lu and Oliver Purcell

THE FIRST COMPUTERS WERE BIOLOGICAL: they had two arms, two legs and 10 fingers. "Computer" was a job title, not the name of a machine. The occupation vanished after programmable, electric calculating machines emerged in the late 1940s. We have thought of computers as electronic devices ever since.

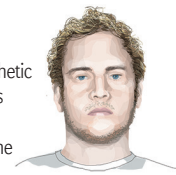
Over the past 15 years or so, however, biology has been making a comeback of sorts in computing. Scientists in universities and biotech start-ups believe they are close to advancing the first biocomputers from mere research objects to useful, real-world tools. These systems, built out of genes, proteins and cells, include basic elements of computer logic: IF/THEN tests, AND and OR operations, even simple arithmetic operations. Some systems include primitive digital memories. Given appropriate biological inputs, these living computers generate (mostly) predictable outputs.

Within about the next five years, the first biological computers might be used as sensitive and accurate diagnostics and therapeutics for human diseases, including cancer, inflammatory diseases and rare metabolic disorders. We and others who are engineering these cellular logic systems envision a future—one not far off—in which they are safe and smart enough to treat disorders as well as identify them. The technology could make it possible to produce complex chemicals, such as biofuels and pharmaceuticals, in novel ways that are faster and less expensive than we can create today. It might allow us to respond to spills by lacing contaminated ecosystems with organisms designed to monitor and degrade toxins.

Illustration by Sam Falconer

Timothy K. Lu is an associate professor leading the Synthetic Biology Group at the Massachusetts Institute of Technology, which integrates memory and computational circuits in living cells, applies synthetic biology to important medical and industrial problems, and builds living biomaterials. He is a recipient of a National Institutes of Health Director's New Innovator Award, among others. In 2014 he co-founded the synthetic biology start-up Synlogic.

Oliver Purcell is a postdoctoral associate in the Synthetic Biology Group at M.I.T. His research spans many areas of synthetic biology, from the design of synthetic biological parts to novel computational approaches for the rational design of biological systems.



That is not to say that biocomputing technology is now advanced. On the contrary, the field is in its infancy. Don't think iPhone—think Colossus.

Colossus was one of the first programmable electronic computers. Had you walked into Bletchley Park, the top-secret codebreaking center north of London where Colossus began operating in 1944, you would have seen it whirring away, paper tape streaming over pulleys, 1,600 vacuum tubes humming. By today's standards, Colossus was laughably primitive. It filled a room—hence the name. It could do only a few kinds of calculations and could not store its own program. It took days or weeks to design, load and test a new program. Operators had to physically rewire the machine each time.

Despite its limitations, Colossus was able to break the encryption the Nazis used to encode their most important messages. That clunky toddler of a computer helped to win a World War. And its descendants propelled civilization, decades later, from the industrial age to the information age.

The most impressive cellular computers made so far are actually much simpler, slower and less capable than Colossus. Like the earliest electronic, digital computers, they do not always work, they run only the simplest programs and they are not reprogrammable outside the laboratory. But we see in this technology some of the same transformative potential for society that digital electronics had in its formative years. Even a tiny bit of smarts, applied cleverly, can create near-magical results in a living system.

Cellular computers are not likely to ever replace the electronic and optical variety. Biology will not win any races against solid-state physics. But the chemistry of life has a unique power of its own, and it can interface with the natural world—much of which, after all, runs on biology—in ways that electronic systems cannot.

SWITCH ON, SWITCH OFF

EVERY CELL in your body is, in some sense, a little computer. The cell receives inputs, often in the form of biochemical molecules attaching to its surface. It processes these inputs through intricate cascades of molecular interactions. Sometimes those reactions affect the activity level of one or more genes in the cell's DNA—that is, how much a given gene is "expressed" by being transcribed into RNA and then translated into multiple copies of the protein molecule the gene encodes. This analog, chemical computation generates outputs: a squirt of hormone from a gland cell, an electrical impulse from a nerve cell, a stream of antibodies from an immune cell, and so on.

As synthetic biologists, we aim to exploit those natural information-processing abilities of cells to run programs that we design. We aspire to go well beyond conventional genetic engineering that just "knocks out" a gene, or cranks up its expression, or inserts a gene or two from one species into cells of a different species. Our goal is to be able to quickly and reliably tailor the behavior of many different varieties of cells (or populations of cells) in much the same way that an electrical engineer designs a circuit board: by choosing standardized parts from a catalog and wiring them together. Unfortunately, biology is different from electronics in ways that frustrate that ambition; more on that later.

The field has made slow but considerable progress. The first big advances came in 2000. That year James Collins and his colleagues at Boston University stitched together two mutually interfering genes to make a genetic switch that can be toggled between two stable states—a one-bit digital memory. In addition, a group led by Michael Elowitz, then at Princeton University, engineered a rudimentary oscillator into a strain of the bacterium *Escherichia coli*. The transformed microbe blinked like a Christmas light as a fluorescence gene turned on and off periodically.

By 2003 Ron Weiss, then at Princeton, had designed a "Goldilocks" biocircuit that causes a cell to light up when the concentration of an environmental compound is just right: not too high, not too low. That system linked together four inverters, which change a HIGH signal to a LOW signal, and vice versa.

A few years later Adam Arkin and his colleagues at the University of California, Berkeley, came up with a heritable form of memory that, when triggered, uses enzymes called recombinases to snip small sections out of the DNA, flip them backward and then put them back into place. The modified DNA segment passes from a cell to its daughters when that cell divides—a useful feature, considering that many bacteria reproduce every hour or two.

Crafting single-operation parts is one thing; cobbling many parts into an integrated system is much trickier but much more useful. Synthetic biologists have created genetic parts to perform all the basic Boolean operations of digital logic (AND, OR, NOT, XOR, and so on). By 2011 two groups of researchers had inserted individual logic gates into bacterial cells and programmed the cells to communicate with one another through chemical "wires," essentially creating multicellular computers.

Martin Fussenegger, Simon Ausländer and their colleagues at the Swiss Federal Institute of Technology Zurich then assembled such parts to create still more advanced systems that could perform simple arithmetic. One of us (Lu), working with

IN BRIEF

Bioengineers have created living cells that can count, add, store data in memory and perform basic logic operations.

These biocomputers communicate using chemical signals, which are inherently noisy. Designers also have trouble predicting how biocomputers will perform before they are built: we simply do not know enough about how cells work.

Research laboratories and companies are testing applications, including ingestible cells that treat metabolic disorders.

Collins, George Church of Harvard Medical School, and others, combined heritable memory units into a cascade to yield an engineered strain of *E. coli* that can count to three. The memory state remains intact in this system from one generation of cell to the next. That is a crucial feature because it allows information about past biochemical events to be stored for retrieval at some reasonably distant time in the future. In principle, the counter we made could be enhanced to reach higher numbers and to record important biological events, such as cell division or cellular suicide.

A FEATURE *AND* A BUG

BIOLOGICAL COMPUTING has begun moving beyond proof-of-concept demonstrations; potential real-world applications are now in sight. Within the past several years we and others have found many ways to engineer sensors, logic operators and memory components into genetic circuits that can carry out truly useful tasks in living cells.

In 2011, for example, a group that included Weiss, now at the Massachusetts Institute of Technology, Zhen Xie, now at Tsinghua University in China, and Yaakov Benenson of the Swiss Federal Institute of Technology Zurich created a far more advanced genetic logic system that can force a cell to self-destruct if it contains a specific cancerous signature. The genetic circuit monitors the levels of six different biological signals—in this case, short pieces of RNA called microRNAs that regulate gene expression. The six microRNA signals form a distinct signature of human-derived cancer cells known as HeLa cells. When the circuit is in a HeLa cell, it triggers a genetic kill switch and produces a protein that directs the cell to commit suicide. In a non-HeLa cell, the circuit is inactive and does not trigger cell suicide.

Other research groups, including our own, have demonstrated biocomputing circuits that can perform basic arithmetic (addition or subtraction), compute ratios or logarithms, convert two-bit digital signals to analog output levels of a protein, and record and transmit the on/off states of all their logic gates from the parent cell to its children.

Last year our group, along with Christopher Voigt's group, both at M.I.T., developed a biocomputing microbe that works inside a mammal's gut. We used mice as test subjects, but the bacterial species we modified, *Bacteroides thetaiotaomicron,* is found naturally and at very high levels in the gut of roughly half of adult humans. Previously, Pamela Silver of Harvard Medical School and her colleagues engineered *E. coli* to operate in the mouse gut.

The biocircuit turns the bacterium into a spy. While the microbe loiters inside the gut, it uses part of its DNA like a notebook to detect whether it has bumped into a predetermined chemical. We targeted innocuous compounds that we could feed to the mice, but the target could easily be a toxic molecule or biomarker present only when the host has a particular disease.

After ingesting the compounds, the mice excrete the surveillance bacteria in their droppings. In those microbes that recorded an exposure to the target, the circuits trigger production of luciferase, an enzyme that glows in the dark. The telltale glow is faint, but we can see it under a microscope.

It is not hard to imagine how such biocomputing systems could be helpful to people who have a gut condition, such as inflammatory bowel disease (IBD) [*see box on next page*]. Soon we may be able to program innocuous, naturally occurring bacteria to seek out and report on early signs of cancer or IBD. The devices could change the color of the stool—or add a chemical to it that is detectable by using an inexpensive kit similar to a home pregnancy test.

THE HARD PARTS OF WETWARE

CELLULAR SENTRIES like those we just described do not need much computational power to greatly improve on the diagnostic tests already available. An IF/THEN test, a few AND and OR gates, and one or two bits of persistent memory are sufficient. That is fortunate because biocomputer engineers face a long list of hard challenges that electronic computer engineers never had to deal with.

Compared with the gigahertz speeds of electronic circuits, for example, biology proceeds at a snail's pace. When we apply inputs to our genetic systems, it typically takes hours for the output to emerge. Fortunately, many biological events of interest do not operate on extremely short timescales. Nevertheless, researchers continue to look for faster ways to compute in living cells.

Communication poses a separate problem. In conventional computers, avoiding cacophony is easy: you simply connect components by wires. When many components have to share a wire, you can give each one its own little window of time to speak or listen by synchronizing each part to a universal clock signal.

But biology is wireless, and there is no master clock. Communication within and between cells is inherently noisy, like radio. One reason for the noise is that biological parts use chemicals rather than physical wires to signal one another. All the components that use any particular chemical "channel" can talk at the same time. What is worse, the underlying chemical reactions that send and receive signals are themselves noisy; biochemistry is a game of probabilities. Designing systems that compute reliably despite noisy signals is a continual challenge.

These issues especially plague biocomputing systems that use analog computing, as many do, because, like slide rules, they depend on values (the levels of proteins or RNAs) that can vary nearly continuously. Digital systems, in contrast, process signals that are either HIGH or LOW, TRUE or FALSE. Although that makes digital logic more robust to noise, many fewer parts are available that work this way.

The biggest problem we face is unpredictability, which is a polite way of saying ignorance. Electrical engineers have numerical models that predict, with near-perfect precision, what a new circuit design will do before they build it. Biologists simply do not understand enough about how cells work—even simple ones like bacteria—to make the same kind of predictions. We feel our way forward, largely by trial and error and often find that when our systems function, they do so only for a while. Then they fall apart. Many times we do not understand why.

But we are learning—and one important reason to build computers out of cells is that this process of building, testing and debugging biological computers can uncover subtleties of cellular biology and genetics that no one had noticed before.

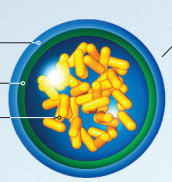
BIRTH OF A NEW MACHINE

IT MAY TAKE DECADES to conquer all these challenges; some, such as the relatively slow speed of biological processing, may be forever intractable. Thus, it seems unlikely that biocomputing will grow in performance at the same exponential trajectory that digital electronic computing did. We do not expect that biological com-

Diagnosis by Biocomputer

Biological computing systems could have myriad applications in agriculture, pharmaceutical manufacturing and medicine. Inserting even a tiny bit of computing logic into a living cell can yield tremendously useful behavior.

Research laboratories are already working, for example, to engineer bacteria that could be safely swallowed as a pill, travel through the digestive system and detect specific signs of disease in the gut. Doctors could then quickly make a reliable diagnosis by placing a swab of the patient's stool into an automated reader. Such technology could remove much of the uncertainty, delay and misdiagnosis that often occurs in gastroenterology.



1 A biocomputing diagnostic for inflammatory bowel disease (IBD) could take the form of a small pill containing millions of bacteria, perhaps from a strain of *Bacteroides thetaiotaomicron,* which normally lives in the human gut. Each bacterium contains multiple computing elements (*described at far right*).

2 An outer protective coating on the pill dissolves away in the small intestine, releasing the bacterial payload into the gut. As the bacteria move through the intestines, the sensors engineered into them are able to detect the simultaneous presence of two or more distinctive biological signals—signals that occur together only when the patient has IBD.

3 As the bacteria move through the colon and into the rectum, the disease signals may disappear from the gut, but memory elements encoded in the bacteria's DNA preserve the information.

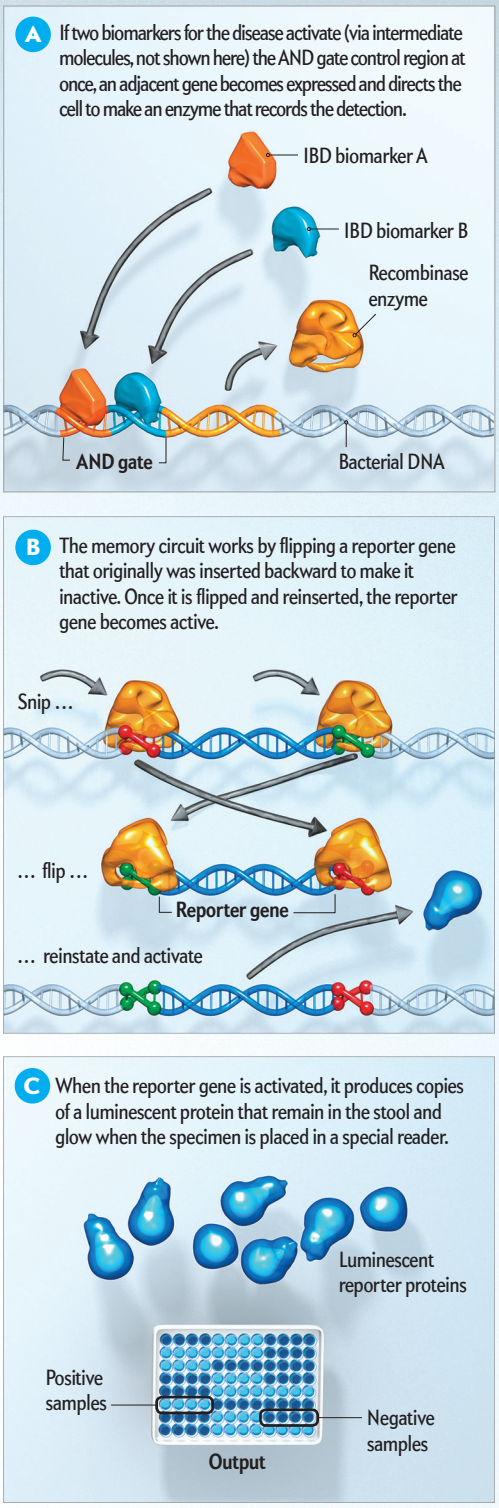
4 The bacteria exit the body along with the rest of the stool. Each engineered cell that detected the diagnostic signal at some point along its journey produces many copies of a luminescent protein that glows faintly and can be detected by an automated reader. The system can provide the information that a patient and doctor need to decide on a treatment.

SCIENTIFIC AMERICAN ONLINE For a list of milestones in biological computing, go to ScientificAmerican.com/apr2016/biocomputing

Illustration by Bryan Christie

How It Works

Bioengineers could transform living bacteria into a diagnostic for inflammatory bowel disease by making just a few small additions to the bacteria's genome. These additions include two sensors that function together as a Boolean AND gate, along with a memory circuit and a gene that yields a luminescent output signal.



puters will ever be faster than conventional computers for mathematical computation or pushing data around. Biocomputer engineers do benefit, however, from an ever accelerating increase in the rate at which we can read and synthesize raw DNA. Like Moore's law, that trend reduces the time it takes us to design, build, test and refine our gene circuits every year.

Although it is still early days, commercially viable applications of biocomputing are coming. Cells can navigate living tissue, discriminate among complex chemical signals, and stimulate growth and healing in ways that no microchip ever could. If biocomputer diagnostics work well, the next logical step is to use them to treat disease when and where they detect it.

Cancer treatment clinics have already started isolating immune system cells known as T cells from patients who have blood cancer, inserting genes into the T cells that direct them to kill the cancer and then injecting them back into the body. Researchers are now working to add logic to the genetic package that gets loaded into the T cells so that they can recognize multiple cancer signatures and be equipped with off switches that doctors can use to control them. Many other kinds of cancer might become treatable by this approach.

In 2013 Collins and Lu got together with several other biologists to found Synlogic, a company to commercialize medicines that use modified probiotic bacteria that can be safely swallowed. The start-up is now refining biocomputers intended to treat phenylketonuria and urea cycle disorders, two rare but serious metabolic disorders that affect people from birth. Animal trials have begun, with encouraging results.

As we gain deeper insight into how the microbiome affects human health, we should find engineered bacteria to be beneficial therapeutics for a widening array of diseases—not just cancer but also inflammatory, metabolic and cardiovascular disorders. With growing experience and an ever increasing library of bioparts, "smart" medicines will become more common and more powerful. Moreover, the technology seems likely to spread from medicine to other areas. In the energy sector, smart bugs may be efficient producers of biofuels. In chemical and materials engineering, biocomputers may prove useful in synthesizing products that are currently hard to make or in exerting just-in-time control over biomanufacturing. In environmental conservation, biocomputers could monitor remote locations for cumulative exposure to toxic substances and then perform remediation.

The field is rapidly evolving—literally. Almost certainly, the most amazing uses of biocomputing have yet to be conceived. SA

MORE TO EXPLORE

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FROM OUR ARCHIVES

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scientificamerican.com/magazine/sa

GIA

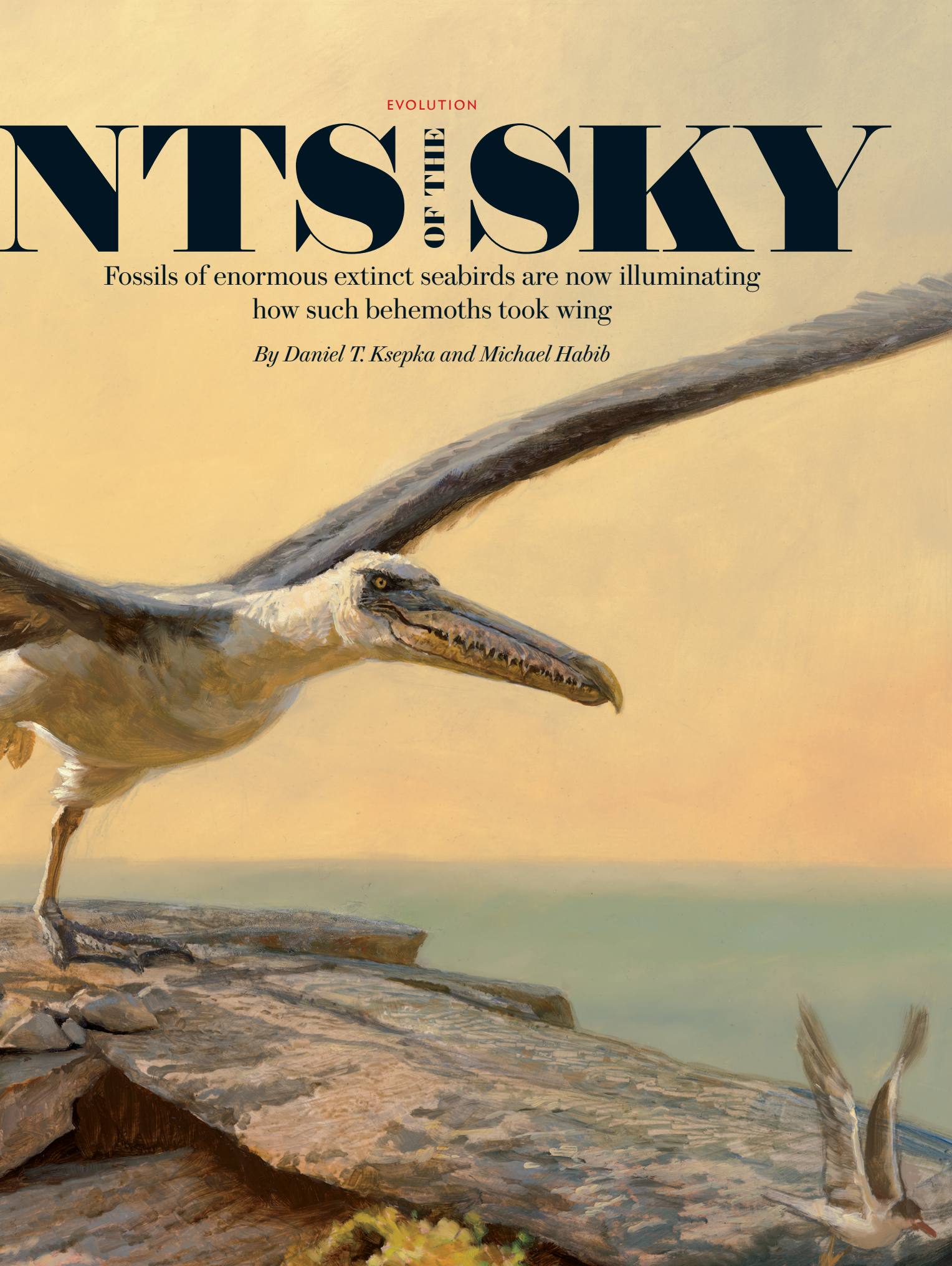
Illustration by James Gurney

EVOLUTION

NTS OF THE SKY

Fossils of enormous extinct seabirds are now illuminating how such behemoths took wing

By Daniel T. Ksepka and Michael Habib



Daniel T. Ksepka is a paleontologist and science curator at the Bruce Museum in Greenwich, Conn. His research focuses on the evolution of birds and reptiles.

Michael Habib is an anatomist at the University of Southern California. He studies the biomechanics of extinct animals, including birds and pterosaurs.

IN ITS MODERN INCARNATION, SOUTH CAROLINA'S PICTURESQUE CHARLESTON HARBOR HOSTS a wide variety of marine birds—from the pelicans and cormorants that forage in its estuaries to the gulls and herons that breed and nest on its offshore islands and the songbirds that pass through en route to warmer climes for the winter months. Around 25 million years ago, however, dragons ruled the Carolina skies. These beasts were not the monsters of medieval folklore, of course, but rather evolution's closest facsimiles, fearsome in their own right: giant flying birds with wings longer than those of some light aircraft and beaks equipped with deadly, spearlike choppers.

The evidence for these terrifying creatures comes from fossils found at Charleston International Airport, appropriately enough. In 1983 a team led by paleontologist Al Sanders, then at the Charleston Museum, unearthed the bones and recognized that they belonged to a large bird. But the researchers had their hands full with other fossils, and the avian bones went into storage. Three decades would pass before an analysis carried out by one of us (Ksepka) revealed just how remarkable the forgotten animal was. Sanders and his colleagues had recovered the largest flying bird on record, a never before seen species belonging to an enigmatic group known as the pelagornithids. Ksepka named the creature *Pelagornis sandersi,* in honor of its discoverer.

For more than 150 years paleontologists have recognized that pelagornithids once patrolled the air. But with only a handful of fragmentary specimens available for study, little was known about how these animals flew, what their lives were like or why they evolved such extreme proportions. Recent analyses of the biggest of them all, *P. sandersi,* along with other studies of colossal avians carried out by the other of us (Habib), have filled in many gaps, helping to paint the most complete picture to date of these astonishing animals. The latest evidence indicates that pelagornithids rose to prominence in the aftermath of the asteroid impact that doomed the dinosaurs and their close relatives the flying pterosaurs and that they may have developed their impressive size as an adaptation to foraging over the open ocean. Whatever the driving force behind their gigantism, they were able to achieve sizes beyond the limits of what some researchers thought was possible for a flying bird.

ENIGMATIC BONES

THE STUDY OF PELAGORNITHIDS has a long, rich history. In 1857 French paleontologist Édouard Lartet described a very large wing bone of one of these birds, which he believed might have belonged to an ancient albatross. He dubbed it *Pelagornis miocaenus,* meaning simply "Miocene seabird." Although the name was uninspiring, the fossil was electrifying and mysterious. The wing bone, a humerus, measured nearly 0.6 meter (two feet) long, indicating that its owner had been a bird twice the size of some modern albatrosses—unthinkable in Lartet's day. Unfortunately, with just that piece of wing to go on, paleontologists had no real clue about what the rest of the animal looked like.

A hint that the owner of the huge bone was not a supersized albatross emerged more than a decade later, in 1873, when English anatomist Sir Richard Owen described the skull of another giant bird, which he assigned to a new species, *Odontopteryx toliapica*. His work made clear that the skull was so distinctive that it could not belong to any of the modern bird groups. Instead it represented a previously unrecognized group of huge extinct birds. The eventual discovery of more complete specimens revealed that Lartet's humerus belonged to this same group.

IN BRIEF

Paleontologists have long known that strange birds called pelagornithids once ruled the skies.

Some pelagornithid species evolved sizes that far exceeded those of the largest modern-day flying birds.

The recent unveiling of a new species in this group—the biggest bird known to have ever taken to the air—has helped scientists figure out how these astounding animals flew and why they evolved giant proportions.

LARGELY COMPLETE SKULL of extinct bird *Pelagornis sandersi,* seen here from various angles, exhibits the distinctive "false teeth" of the pelagornithid family of birds. The teeth are hollow projections formed from bone and would have helped the predatory *P. sandersi* grasp prey.

COURTESY OF CHARLESTON MUSEUM

Additional discoveries came to light slowly over the next century, sometimes vanishing soon afterward. In 1910 one of the most complete pelagornithid skulls ever found was attributed to a new species, *Pseudodontornis longirostris*. The University of Königsberg in Germany had purchased the skull from a Brazilian sailor. But during World War II, Allied bombing devastated Königsberg, which was annexed by the Soviet Union and renamed Kaliningrad at the end of the war. Today the fossil's whereabouts are unknown; no one is sure if it was destroyed in the conflict, stolen or removed to another location.

In the decades that followed, fossil hunters discovered more pelagornithid species, including *Pelagornis orri* from California and *Pelagornis chilensis* from Chile. Whereas most of the earliest finds were scrappy, partial skeletons from these new species allowed scientists to begin piecing together a more detailed understanding of how these animals were built and what kinds of activities they were adapted to perform.

The emerging picture defied imagination. Foremost on the long list of unusual features of pelagornithids are the serried ranks of toothlike structures that line their upper and lower jaws. Birds lost the ability to form teeth more than 65 million years ago. But pelagornithids evolved a work-around. Unlike true teeth, which are composed of enamel and calcified tissue known as dentine and are set in sockets, the so-called pseudoteeth of pelagornithids were hollow projections formed directly from bone. These pseudoteeth were arranged in orderly, repeating sets of size classes in the best-known species. A pair of short, thin, needlelike pseudoteeth flanked each of the medium-sized projections, and a pair of these three-tooth packages in turn flanked the tallest, conelike pseudoteeth. In life, a thin layer of the same material that sheathes the beak of modern birds probably covered the bony teeth. The overall effect was that of a menacing grin rippling with spikes adapted to nabbing and holding onto prey.

Other weird traits further enhanced the hunting prowess of pelagornithids. The skull of these birds was uniquely flexible. Its midpoint had a strong hinge that permitted bending at the spot where the braincase met the upper beak. Additionally, the lower jaw had a joint built into the midpoint of the left and right sides.

It's a Bird, It's a Plane

Recent analyses of the *P. sandersi* bones, which were discovered decades ago on airport grounds, showed that this creature is the biggest flying bird on record—more than twice the size of the modern record holder, the wandering albatross. In fact, *P. sandersi* is bigger than some experts had thought possible for a volant bird. But it possesses several key adaptations to air travel (*right*). Comparing this animal's proportions with those of living birds helped researchers to reconstruct its flight style (*below*).

Shoulder

The shoulder blade is incredibly small compared with the rest of the body, which suggests the muscles attaching to the wing from the back became highly reduced as the need for flapping flight diminished. In addition, the unusual, almost square shape of the head end of the humerus prevented rotation at the shoulder joint, which hindered flapping but helped to stabilize the wing during gliding flight.

Long and Lean

Factors that determine flight style in birds include aspect ratio (the ratio of the wing's length to its width), wing loading (the weight each square centimeter of wing has to support) and wing shape. *P. sandersi* had high aspect ratio, pointed wings and intermediate wing loading like an albatross, suggesting that the extinct giant would have excelled at soaring long distances over oceans.

P. sandersi

Argentavis

This extinct species, which previously held the title of largest known flying bird, is inferred to have had condorlike wings with low aspect ratio and slotted wing tips.

Illustrations by Raúl Martín (P. sandersi) and Daisy Chung (silhouettes)


Wing
The bones were paper-thin but stiff—a combination that would have cut down on the bird's weight while resisting gusts in windy conditions.
Hind limb
Although its short legs would have made terrestrial locomotion awkward, *P. sandersi* could have sprinted short distances on land to launch itself into the air. With its presumably webbed feet, the animal seems to have been better adapted to running takeoffs from water, however.
Magnificent frigate bird
High aspect ratio and low wing loading optimize this bird for slower, higher-altitude soaring than albatrosses engage in. Frigate birds cruise as much as 2.5 kilometers above sea level; albatrosses fly close to the waves.
Great bustard
This species is one of the heaviest living flying birds. Its weight and long, wide wings mean its aspect ratio and wing loading are somewhat intermediate. It uses a very slow, regular flap cycle in the air.
House sparrow
Low aspect ratio, intermediate wing loading and rounded wings let this bird maneuver in closed spaces.
California condor
Low aspect ratio, intermediate wing loading and broad, slotted wings make for a bird that excels at soaring on hot air rising from land.
Mallard duck
High aspect ratio, high wing loading and pointed wings impart speed but not maneuverablility. As a result, it is efficient in migratory flight but cannot escape a falcon or land gracefully on the ground.
Ruby-throated hummingbird
Among the smallest living birds, it has low aspect ratio, high wing loading and short, butter-knife-shaped wings that it uses in a highly specialized way to hover.
Ruffed grouse
The short, broad, rounded wings of this species add up to low aspect ratio and high wing loading. As a result, this bird can take off rapidly to flee predators but cannot fly efficiently over longer distances.
Wandering albatross
With its high aspect ratio, intermediate wing loading and pointed wings, this bird is a good example of a marine glider. It is the closest thing to *Pelagornis* that is alive today.
Common swift
With wings shaped like an albatross's, this much smaller bird engages in continual "fluttering" flight higher up in the air and mostly over the land.

It seemed inconceivable that fossils of such enormous size could even belong to a bird.

Instead of solid bone, the jaw was held together at the "chin" by a flexible ligament. Together these traits would have enabled substantial bending of the jaws, perhaps to accommodate large prey.

Bones from below the head also distinguish pelagornithids from other avians. The wing bones of these birds are so flattened that some paleontologists actually arranged one of them, the humerus, upside down in past skeletal reconstructions. Although all flying birds have hollow bones, which make their skeletons structurally efficient, pelagornithids took that trend to extremes. All their wing elements exhibit exceptionally thin bone walls. This thinness means the birds retain the bone stiffness they need with a minimum of weight—critical for giant flying animals. But lightly built bones have a downside: an unexpected collision might spell doom because such bones are easier to fracture. A break in one of them would ground the bird, leaving it unable to feed.

The leg bones are arguably the most normal part of pelagornithids, at least in terms of their shape. Yet they are almost comically small compared with the wing bones. Nevertheless, the hind limb bones had reinforced walls and a stout shape that would have made them relatively strong. Like many living seabirds, pelagornithids were probably somewhat awkward when it came to crossing large distances on land. But all they needed, presumably, was the ability to sprint effectively for short distances to initiate takeoff.

RECORD BREAKER

BY THE TIME *P. SANDERSI* was finally described in 2014, scientists had already established that the pelagornithids were highly unusual birds. But *P. sandersi* one-upped even that strange company. Its humerus alone measured nearly a meter (around three feet) in length—more than a third longer than Lartet's original pelagornithid humerus and even longer than the entire arm of an average person. It seemed inconceivable that fossils of such enormous size could even belong to a bird. Indeed, some research suggested a theoretical limit of 5.1 meters for wingspan in a marine soaring bird, beyond which an animal simply would be too heavy to remain aloft by flapping. Yet the limb bones found at the Charleston airport clearly represented an avian wing and leg, as indicated by their telltale wafer-thin walls, which needed careful treatment with chemical hardening agents to keep them from crumbling into shards. And there was no mistaking the accompanying skull, with its trademark pseudoteeth, for anything other than a pelagornithid.

The excellent preservation of these skeletal elements, combined with insights from other pelagornithid specimens, allows for a detailed reconstruction of *P. sandersi*. In life, the feathered wings of this bird would have measured an estimated 6.06 to 7.38 meters (20 to 24 feet) tip to tip—the largest wingspan of any bird on record, living or extinct, and more than double the average wingspan of the largest modern flying bird species, the wandering albatross. Extrapolating from the circumference of the weight-bearing leg bones, *P. sandersi* would have tipped the scales at somewhere between 21.9 and 40.1 kilograms (48 to 88 pounds)—the weight of a golden retriever. Although massive compared with modern fliers, the animal was dainty for its wingspan, thanks to its small body and ultralightweight skeleton.

Proceeding from those parameters, we have worked out how this magnificent creature and other giant pelagornithids flew. Estimating the locomotor capabilities of extinct animals is a tricky exercise, but researchers today have better tools than ever before to do so. Key observations from living birds, along with fundamental physical principles from aerodynamics, informed our proposed flight scenario.

Today's flying birds exhibit a wide variety of flying styles, such as the hummingbird's hovering and the seagull's slower flapping flight. Right away the incredibly long wings of *P. sandersi* and other pelagornithids suggested that their primary mode of flight was soaring, in which the wings do not flap to generate lift but instead are held outstretched to use energy from wind or rising air. Modern soaring birds have a few different ways of remaining aloft for long periods, though, and figuring out what strategy pelagornithids employed required deeper analysis.

Species such as condors and vultures possess broad wings relative to their body weight, which creates what is termed low wing loading—that is, each square centimeter of wing is required to support relatively fewer grams than would be needed in a bird of comparable mass but less expansive wings. The wings of these birds also have slotted tips, meaning that the feathers at the tip of the wing can spread apart, reducing drag. The combination of low wing loading and slotted wing tips enables these animals to surf currents formed by warm air as it wafts up from land. And it allows them to do so with relatively shorter wings than seabirds have, which comes in handy when navigating environments with obstacles such as cliffs and vegetation.

Frigate birds pursue a second type of soaring, traveling on thermals that form over ocean rather than land. They have more slender, tapered wings with pointed, rather than slotted, tips. They are also among the most lightly built of all birds and thus exhibit exceptionally low wing loading. These traits aid frigate birds in traveling long distances while cruising high up in the sky, ready to swoop down to capture prey near the sea surface.

At the other end of the marine soaring spectrum are the albatrosses, which also have very long, narrow wings with pointed tips. Albatrosses, however, are heavier relative to their wing area, which means they need strong, fast winds to power their flight. Albatrosses fly by harnessing the wind gradient above the waves. They fly into the slower wind near the surface of the water to gain altitude and then curve around to ride the stronger winds back down to sea level, endlessly looping to gain altitude and trade it for distance in a maneuver called dynamic soaring. In 2004 an albatross outfitted with a tracking device was clocked moving an average of 127 kilometers an hour for nine hours straight—the record sustained soaring speed for any living animal. It was riding winds from an Antarctic storm.

Improved knowledge of pelagornithids from spectacular

SCIENTIFIC AMERICAN ONLINE Watch a video on how artist James Gurney painted *Pelagornis sandersi* at ScientificAmerican.com/apr2016/birds

specimens like that of *P. sandersi* suggests that these birds specialized in a form of soaring not seen among today's soaring birds. Their wings were narrow but still large in area thanks to their great length. In other words, evolution gave these birds the best of two worlds: their large overall size would have allowed them to use dynamic soaring when winds were strong, and with their large wing area and high aspect ratio, they would have also excelled at cruising over quiet oceans for thousands of kilometers at a time. The biggest pelagornithids would have been able to cover those distances relatively rapidly: we calculated that the speed of optimal efficiency for these giants would have been more than 40 kilometers an hour, putting them well ahead of the pace attained by world record holder of the 100-meter dash, Usain Bolt, who broke the ribbon at 9.58 seconds—equivalent to running 37.6 kilometers an hour. Moreover, *P. sandersi* could have maintained that pace with relatively little effort: after gaining 45 meters of altitude, the bird could glide for more than a kilometer without any flapping or assistance from winds.

Although *P. sandersi* probably spent most of its time on the wing, it would have to land occasionally (to nest, for example), which would also mean taking off again. The tiny legs of large pelagornithids originally led some researchers to question the ability of these large birds to launch effectively. But with the discovery of more complete behemoths, including *P. chilensis* and *P. sandersi,* it became apparent that the hind limbs were actually well proportioned to the relatively compact bodies of these giant birds. The first ever quantitative analysis of launch mechanics in giant pelagornithids, presented by Habib at a premiere international paleontology meeting, found that the short, stout hind limbs of *Pelagornis* were appropriately shaped and positioned for brief sprints, especially over water surfaces (the feet in *Pelagornis* were most likely webbed). The bones of the hind limbs were also sufficiently strong to support significant muscle mass, able to propel the modest-sized bodies (with their oversized wings) up to launch speeds. These leg traits would have made *P. sandersi* an excellent water launcher, even if it was probably relatively poor at walking over land.

A VACANT NICHE

THE DISCOVERY OF *P. SANDERSI*—a titan among what were already considered to be exceptionally large birds—raises the question of why giant size evolved in flying avians. Gigantism is not universally advantageous in biology. Big animals need more food than small ones, they may require larger areas for nesting and they tend to have smaller population sizes than modestly proportioned species. Yet despite those drawbacks, multiple successful lineages of giant fliers have evolved over the course of the earth's history. In fact, the lack of truly enormous fliers today is the exception to the rule: giant flying animals darkened the skies for most of the past 120 million years.

It turns out that large size has considerable upside. For one, it improves the efficiency of long-distance flight because bigger fliers use less energy per unit distance covered than their small counterparts do. Larger animals can also capture (or steal) prey that smaller fliers cannot handle. Furthermore, large flying animals have limited predation risk—once airborne, a big flier is almost immune to attack from predators.

For millions of years the winged reptiles known as pterosaurs ruled the airspace over land and sea. Those living over the oceans probably fed on invertebrates and fish, and they had body plans well adapted to long-distance ocean voyages. They were very successful. But the same asteroid impact that extinguished the dinosaurs (apart from birds, which are living dinosaurs) also did in the pterosaurs. With their extinction, competition in several realms suddenly plummeted, and the ecological "niches" they had occupied opened up. One of these niches was that of the large, marine soarer.

Pelagornithids appear to have filled this role, debuting approximately 10 million years after the last pterosaurs. Their fossils come almost exclusively from sedimentary deposits in ocean environments, indicating that marine prey formed the mainstay of their diet. Because their pseudoteeth were not very strong compared with true teeth, some paleontologists speculate that soft-bodied animals such as squid and eels found near the ocean surface may have been the primary food source. Other, more ill-gotten morsels may also have been on the menu. Today large marine birds often bully other species into relinquishing their food, sometimes even harassing other birds in flight until they vomit up their prey, as the skua does. By far the largest birds in their ecosystems, pelagornithids may well have harangued smaller seabirds to rob them of meals. They also could have snatched chicks from their nest, a predation behavior practiced by modern giant petrels, skuas and even some pelicans.

Pelagornithids were not the only large birds to help fill the roles vacated by pterosaurs: another group of large flying birds, the teratorns, appeared about 23 million years ago and survived all the way up to the end of the Pleistocene epoch, 11,700 years ago. With their shorter, broader wings and heavier bodies, they probably flew and hunted more like condors.

After soaring over the seas for more than 50 million years, pelagornithids vanished completely roughly three million years ago during the Pliocene epoch. The root cause of their disappearance remains a mystery. The Pliocene witnessed profound changes in the oceans as the Panama land bridge closed, sundering a major connection between the Atlantic and the Pacific and radically altering currents. Yet it is hard to imagine even this event ending a lineage that had survived so many previous shifts in climate, ocean circulation and fauna.

Perhaps overspecialization played a role in the demise of pelagornithids. Early in the radiation of this group, several "small" species, which reached the size of modern albatrosses, evolved. Over time these diminutive forms died out, and for the last half of pelagornithid history only giant species remained. These behemoths may have relied more heavily on specialized feeding strategies and global wind currents than smaller marine birds did—and ultimately became victims of their own success. SA

MORE TO EXPLORE

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Flight Performance of the Largest Volant Bird. Daniel T. Ksepka in *Proceedings of the National Academy of Sciences USA,* Vol. 111, No. 29, pages 10,624–10,629; July 22, 2014.

FROM OUR ARCHIVES

Winged Victory. Gareth Dyke; July 2010.

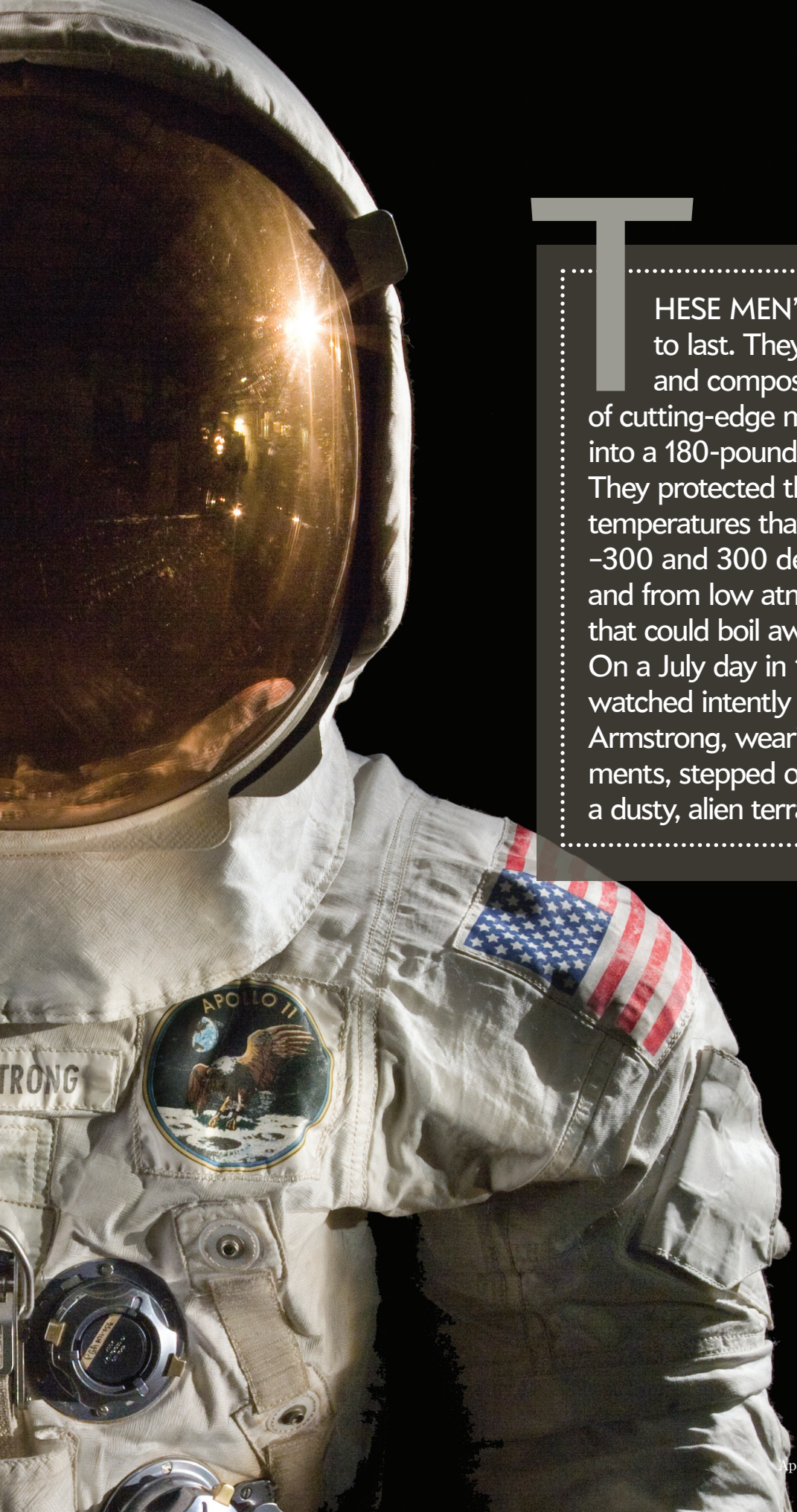
CHEMISTRY

The Art of Saving Relics

Plastic in Apollo spacesuits, Andy Warhol paintings and other museum pieces is falling apart. Researchers are learning how to rescue the endangered treasures

By Sarah Everts

MESSY HERITAGE: At the Smithsonian National Air and Space Museum, the polycarbonate visors of Apollo spacesuits are degrading as they leach out additives.



THESE MEN'S SUITS were built to last. They were pristine-white and composed of 20-plus layers of cutting-edge materials handcrafted into a 180-pound frame of armor. They protected the wearers from temperatures that fluctuated between –300 and 300 degrees Fahrenheit and from low atmospheric pressure that could boil away someone's blood. On a July day in 1969, the world watched intently as astronaut Neil Armstrong, wearing one of these garments, stepped off a ladder and onto a dusty, alien terrain, forever changing

the landscape both of the moon and of human history. Few symbols of vision and achievement are more powerful than the Apollo mission spacesuits.

Back on Earth, the iconic garments found new lives as museum pieces, drawing millions to see them at the National Air and Space Museum in Washington, D.C. And staff members there have found, to their surprise, that the suits need their own life support. They are falling apart.

Last year Lisa Young, a conservator at the museum, noticed that a white, foggy bloom was beginning to creep across the transparent fishbowl helmets and that their smooth, curved surface was beginning to crack. "It is really frustrating," Young says. "We had thought they were relatively stable." There had been warning signs of suit trouble, though. The neoprene pressure bladders that kept astronauts' bodies from exploding in the vacuum of space began crumbling years ago, releasing acidic gases. "Anybody who has worked with the spacesuits knows their smell," Young says. "I'd describe it as slightly pungent sweet chlorine." And an orange-brown sticky stain began appearing on the exterior white fabric.

The trouble is the construction material: plastic. Most people think plastics last forever, which makes them a bane to the environment. But although the repeating units of carbon, oxygen, hydrogen and other elements in plastics have a long lifetime, the overall chains—synthetic polymers—do not age well. Light conspires with oxygen and temperature to weaken the bonds that hold the units together. Then chemicals added to plastics to make them bendable or colorful migrate outward, making the surface sticky and wet and perfect for attracting dirt. The polycarbonate spacesuit visor, Young thinks, was leaching out a substance added to make it easier to shape.

Priceless 20th-century art is in serious trouble as well. In that era, Andy Warhol, David Hockney and Mark Rothko all used acrylic paint—a plastic polymer popularized in the 1940s as an alternative to traditional oil paint. Plastic is, in fact, a building block of much of our recent cultural heritage, including important designer furniture, archival film, crash test dummies, the world's first Lego pieces and Bakelite jewelry, as well as the plastic sculptures made by the pop-art movement. "We now know that objects made of plastic are some of the most vulnerable in museum and gallery collections," says Yvonne Shashoua, a conservation scientist at the National Museum of Denmark and one of the first cultural heritage researchers to study plastic degradation.

The conservation field is now racing against time, trying to keep pace with the material's unexpectedly rapid deterioration. Conservators have identified the most trouble-prone plastics. Scientists are developing new tools to diagnose plastic degradation before it becomes visible to the human eye—for example, by measuring the molecules wafting off artifacts. Researchers are also devising new strategies for freshening up precious plastic art without harming it, using everything from cleaning solutions called microemulsions to polyester microfibers that gently remove dirt.

Sarah Everts is the Berlin correspondent for *Chemical & Engineering News*. She writes regularly about science and art conservation and is working on a book about the science of sweat.

DEGRADING DENIAL

THE REALIZATION that plastics were a problem dawned slowly. For most of the 20th century the museum world was afflicted with "plastics denial syndrome," Shashoua says. "Nobody thought that plastic objects in their collections would degrade." In fact, some conservators were so enamored with plastic during its heyday of the 1950s, 1960s and 1970s that they used the polymers in ill-advised ways themselves. For example, conservators laminated Belgium's oldest parchment, the Codex Eyckensis from the eighth century A.D., with PVC plastic for protection. Decades later this laminate had to be painstakingly separated from the parchment because changes in the PVC began exacerbating the ancient document's demise.

Crash test dummies first made Shashoua think plastic was not forever. She had grown up visiting London's Science Museum, where dummies built in the 1970s to better understand the human toll of automobile collisions were on display. The mock bodies—among the first of their kind—have a metal frame skeleton enveloped by medical gelatin that has been sculpted into human form and then covered by a layer of protective PVC. During impact tests, encapsulated red paint would bleed out of the gelatin bodies and get caught underneath the PVC layer wherever the dummy had smashed against a car frame during collision experiments. The red wounds indicated the body's most vulnerable regions.

As the decades passed, these same crash test dummies in the museum began bleeding again. Shashoua was shocked to see that the PVC covering these artifacts was collapsing, dripping so much wet, sticky muck that museum staff had set up petri dishes in the showcase to collect the mess. When Shashoua was put in charge of cleaning the artifacts in 2011, she noticed that the dummies' sculpted contours were losing their definition as the PVC plastic collapsed; in some parts, the red paint mixed with the wounded plastic, giving the goo dripping from the dummies an eerily realistic brownish-red tinge.

IN BRIEF

Much of our modern cultural heritage, from acrylic paintings to Legos to spacesuits, is made of plastic chemicals.

Plastics do not last forever but deteriorate into messy molecular fragments, and this instability can ruin paintings and other important objects.

Conservators have new methods to identify early warning signs of decay and to clean the disintegrating art, tailoring the technique to the underlying chemistry.

PRECEDING PAGES: COURTESY OF SMITHSONIAN NATIONAL AIR AND SPACE MUSEUM

DIRTY PICTURE: Andy Warhol used acrylic, a polymer, in his painting of Brooke Hayward (*left*). A museum used a portable atomic force microscope (*right*) to ensure cleaning did not damage the fragile surface.

This dripping mess—and in fact, all kinds of plastic degradation—owes its start to oxygen. With help from light and heat, the gas rips off the electrons from the long polymer chains that entwine to form a plastic object. Losing electrons can weaken and break chemical bonds in a plastic, undermining its structure. Essentially the long chains break up into smaller constituent molecules called monomers. In the case of the crash test dummies, this destabilization allowed ingredients called plasticizers, which are added to make the plastic supple, to pour out.

When the museum world began to realize that plastics were not invincible to time, those tasked with protecting plastic art and artifacts had to start from scratch to understand in detail why their collections were breaking down, says Matija Strlič, a conservation scientist at the Institute for Sustainable Heritage at University College London. Although there was extensive literature on polymer production, this research stopped at the end of a plastic object's expected lifetime—right when conservators get interested, Strlič says. Polymer makers had probably expected that old plastic objects would get tossed away, not delivered to museums.

THE FEARED FOUR

CONSERVATORS LEARNED that four kinds of plastic polymers are especially prone to problems: PVC, found in everything from spacesuit life-support tubing to crash test dummies; polyurethane, a primary ingredient in products as diverse as panty hose and packing sponges, as well as sculptures made from these materials; and finally cellulose nitrate and cellulose acetate, two of the world's first industrially produced synthetic polymers, found in the film used in early cinema and photography, as well as in artificial tortoiseshell items, such as vintage combs and cigarette holders.

Cellulose acetate and cellulose nitrate are not only fragile, they are also often referred to as "malignant" by conservators, Shashoua says. That is because they spread destruction to nearby objects. As their polymer networks collapse, they release nitric acid and acetic acid as gases. (Acetic acid is what gives vinegar its characteristic smell and degrading film an odor reminiscent of salad dressing.) The acids eat away at objects made of these plastics. To make matters worse, their gases can also corrode metal and textile things in the same display case or nearby storage. That smell of vinegar is not just an alarm bell that these objects are destroying themselves but that the degrading polymer is taking down innocent bystanders as well.

Shashoua has seen fashion display cases where the acids from a degrading plastic comb have begun eating away textile outfits showcased with the comb or where the plastic in faux tortoiseshell eyeglass frames releases acid that corrodes the spectacles' metal hinges. Once, in her own work space, a box containing knives with cellulose nitrate handles began releasing nitric acid that corroded both the metal blades and the hinges of a cupboard near where the utensils were being stored, Shashoua says. To stop these chemical attacks, conservators may put objects made of cellulose acetate in well-ventilated spaces to whisk away the dangerous gases. They also capture the poisonous gases in the tiny pores of filters made from activated carbon and zeolite, in much the same way gas masks protect troops exposed to chemical weapons.

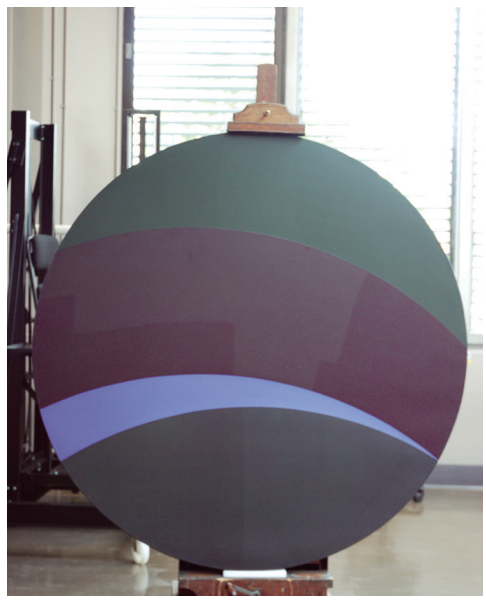
Ventilation and trapping are good strategies against cellulose acetate and cellulose nitrate, but the methods do not work on all plastics, Shashoua says. For example, when PVC breaks down, if its degradation products are pulled away from the surrounding environment, the plastic just releases more. Instead conservators need to keep PVC locked down, sealed in airtight containers, to stall its demise. When conservators noticed that the pristine-white Apollo mission spacesuits were getting orangey-brown stains on their nylon exterior, they realized the cause was plasticizer leaching out of life-support tubing made of PVC that had been sewn into the textile. The tubing kept astronauts' bodies from overheating by circulating cooled water around the outfit. "We had to carefully remove all the life-support tubing from all the Apollo suits and store it separately in sealed containers," Young says. "That was a lot of work."

These opposing approaches—sealed containers versus ventilated ones—highlight why there is no one-size-fits-all solution. "No two objects are alike," Strlič says. For this reason, conservation scientists try to identify the base polymer in a plastic artwork or artifact, typically with analytical machines such as a Fourier transform infrared spectrometer, which bounces long wavelengths of light off an object to reveal its unique molecular

fingerprint. Conservators at the Solomon R. Guggenheim Museum in New York City used such a method to uncover a hidden danger in artwork by Bauhaus pioneer László Moholy-Nagy. They had believed the base material for his painting *Tp2* was Bakelite (a phenol-formaldehyde resin), says Carol Stringari, head of conservation at the museum. But recent infrared spectrometer analysis by scientists affiliated with the Art Institute of Chicago revealed that the polymer was actually cellulose nitrate, one of the plastics that can release harmful gaseous acids.

Spectrometry used in this way is helpful, but it has limits. It can identify many ingredients, but it does not always show the entire potpourri of dyes, stabilizers, surfactants, plasticizers and antioxidants that are mixed into plastics. Often industrial manufacturers keep these recipes secret as part of their intellectual property. Because there is no easy reference for their components, it requires arduous analysis to uncover the plastic's chemical makeup.

These additives change the way an object will age and fall apart. Some varieties of PVC, such as the kind in the spacesuit's life-support system, break down by leaching a sticky plasticizer called di(2-ethylhexyl)phthalate. Other PVC objects degrade by developing a white, powdery crust on the surface: in this case, stearic acid is to blame. It is a lubricant added to the plastic to prevent the polymer from sticking to its mold during the manufacturing process.



WET WORKS: The acrylic painting *Andromeda* (*above*) had additives that grew into a light-colored bloom, but conservators (*top*) modified ions and salt levels in water to strip away the discolored chemicals and leave the dark paint intact.

SNIFFING OUT DECAY

IT IS SO IMPORTANT to identify the chemical mélange before developing a life-extension strategy that researchers are literally sniffing out the ingredients in plastic artifacts. For example, in a project aptly named "Heritage Smells," Katherine Curran of University College London capitalized on the fact that a lot of degrading plastics emit stinky molecules. Not only does cellulose acetate smell like vinegar as it breaks down and aging neoprene like sickly sweet chlorine, but many other plastics also release volatile molecules as they disintegrate: degrading PVC has the aroma of a new car, and degrading polyurethane can smell like raspberry jam, cinnamon or burning rubber. These are just the odors detectable by the human nose. Curran developed a mass spectrometry technique that analyzes all the volatile molecules rising off plastic objects to pinpoint the additives and stabilizers breaking down in a plastic. The goal is to identify what is going on inside without needing to take a sample and to do so before there are visible signs of decay, Curran says.

Curran took her technique to the Birmingham Museum & Art Gallery, where she sampled the air around an enormous art installation made in 2005 by Benin artist Romuald Hazoumé called *ARTicle 14, Débrouille-Toi, Toi-Même!* which translates to *ARTicle 14, Straighten Yourself Out, by Yourself!* It features a market cart full to the brim with sports shoes, computers, a film reel, golf clubs, old Nokia phones, toys, pots, pans, high-heeled pink shoes and a vacuum cleaner, to name just a few components in the piece, which Hazoumé put together from objects he had collected during the 1990s and 2000s. Amid the chaotic artwork, Curran and her colleagues detected the presence of acetic acid, one of those corrosive gases that can hurt nearby materials. "We found that the film reel—specifically, degrading polyester in the film—was emitting the acid," Curran says. Museum staff are now considering whether to store the film reel separately or use absorbents for the acid to prevent it from having a detrimental effect on other components of the piece, she says.

Curran has also tried out her canary-in-a-coal-mine technique at the Museum of London on a collection of vintage handbags—purses made of faux leather, mock tortoiseshell, or coiled, 20th-century telephone cords. In the case of the white-telephone-cord purse, Curran sniffed out the presence of plasticizers that typically emerge from degrading PVC—a useful alarm bell for staff who may want to store the purse in a sealed container.

Researchers are also turning to new imaging technologies that create detailed two-dimensional maps of the chemical composition of an object, essentially going pixel by adjoining pixel. For example, Strlič has combined near-infrared spectroscopy with a digital camera to produce two-dimensional colored maps from which conservators can identify the molecular makeup of artifacts that contain many types of plastic, as well as the migration of degradation chemicals. Strlič has gazed inside a popular vintage piece from the 1950s called a crinoline lady—where a plastic bust of a woman forms the handle of a hairbrush. Strlič's team used the technique to identify the handle as cellulose acetate and the brush hair as nylon, using color gradients to show the location of the two plastics in the artifact.

SCIENTIFIC AMERICAN ONLINE Learn how a new project explores nanotechnology to restore art at ScientificAmerican.com/apr2016/nano-restart

By identifying potential dangers such as the acetate, museum staff might be able to take action before damage is visible to the naked eye.

Although researchers are getting better at diagnosing how a plastic artifact or artwork is degrading, they are still trying to figure out how to best stop the decay and repair damage. That was one challenge tackled by a project called POPART, or the Preservation of Plastic ARTefacts in Museum Collections, which started in 2008 and combines efforts from institutions around the world. Cleaning may make the object look better, but it might eventually accelerate the overall demise. A white crust on the surface might be unsightly but is also a protective patina, similar to the green oxidized layer that forms over aged copper as both a degradation product and a protective skin.

CLEANING UP

EVEN IF WASHING OFF this patina is the right strategy, POPART researchers want cleaning methods that can do so safely. Conservators are very cautious—a good characteristic in those charged with caring for million-dollar art. And plastics can get cracked, dissolved or discolored when exposed to the wrong cleaning agent. POPART investigated approaches ranging from high-tech microfibers and ultrasound to carefully formulated cleaning microemulsions (solutions of water, oil and a surfactant that lifts dirt), as well as gels. The scientists learned that cleaning a polystyrene object with acetone—often used in nail polish remover—could turn the plastic from transparent to opaque and eventually dissolve it. Isopropanol, a different alcohol-based cleaning solvent, however, is safe for most plastics.

Using something as simple as water to clean acrylic paintings turns out to be risky, says Bronwyn Ormsby, a conservation scientist at the Tate, a group of four museums in England. She confronted that problem with the 1962 painting *Andromeda,* the Tate's oldest acrylic piece. Russian-American artist Alexander Liberman painted this abstract, geometric work on a circular canvas; its four solid colors—black, lilac, dark purple and dark green—evoke the darkness of outer space. But acrylic paints have additives called surfactants that help to keep pigments suspended in the paint tube rather than settling to the bottom. That is good for the painter. Yet once on a dried canvas, these surfactants migrate to the surface and create a sticky substance that attracts dirt. By 2007 *Andromeda* was obscured by so much surfactant buildup that the painting had "a whitish bloom, which is quite distracting on paintings with dark colors," Ormsby says. Ordinarily, she would turn to water as a cleaner: "Water often removes soil better than any other solvent." But water also makes acrylic paintings swell. That can lead to a loss of paint during the cleaning process.

Water can be tweaked to make it safer, though. Investigators led by Richard Wolbers of the University of Delaware have found that keeping water's pH levels around 6 and making the water moderately salty can limit the swelling of acrylic paint. Ormsby used that technique on the Liberman painting, which today looks as dark and lonely as it did five decades ago. Researchers at the Tate have also used an atomic force microscope to monitor Warhol's acrylic portrait of Brooke Hayward as it was cleaned, to make sure dirt and not paint was being removed.

SUSTAINABLE ART

ORMSBY AND OTHERS are also working with scientists at Dow Chemical to use the company's industrial-scale abilities to run a large number of chemical reactions quickly to test a variety of microemulsions on acrylic paint samples. Their goal is to try different combinations of cleaning compounds to find the best formula for washing painting surfaces without harming them.

Plastics researchers are also reaching out to artists to let them know about the potential pitfalls of producing art from plastic. "The idea is not to interfere with the creative process but to allow the artists the option to use this information if they wish to," says Carolien Coon, who is an artist herself, as well as a conservation scientist at the U.C.L. Institute for Sustainable Heritage. Coon says she wonders about a sculpture she sold years ago that was made of silicone rubber, a bronze cast, a fishbowl and baby oil. "I have no idea how it looks today. I hope it hasn't leaked all over the dining-room table."

Using something as simple as water to clean acrylic paintings turns out to be risky; it can lead to paint loss.

The great hope of conservation scientists is that restoring the past will also help them prepare for the future, when today's plastic materials—such as 3-D-printed objects—start entering museum collections. One such item might be the first 3-D-printed acoustic guitar or a retired International Space Station suit. Eventually all will be past their prime, and conservators want to have the tools in hand to give these cultural icons a face-lift. SA

MORE TO EXPLORE

The Science of Saving Art: Can Microbes Protect Masterpieces? Katherine Harmon in ScientificAmerican.com. Published online February 9, 2009. www.scientificamerican.com/article/the-science-of-saving-art

Plastic: Has the Dream Material of the 20th Century Become the Nightmare of the 21st? Yvonne Shashoua in *Incredible Industry: Preserving Evidence of Industrial Society.* Edited by Morten Ryhl-Svendsen, Karen Borchersen and Winnie Odder. Proceedings of the Nordic Association of Conservators' 18th Conference, Denmark, May 25–27, 2009.

Assessment of the Degradation of Polyurethane Foams after Artificial and Natural Ageing by Using Pyrolysis-Gas Chromatography/Mass Spectrometry and Headspace-Solid Phase Microextraction-Gas Chromatography/Mass Spectrometry. A. Lattuati-Derieux in *Journal of Chromatography A,* Vol. 1218, No. 28, pages 4498–4508; July 15, 2011.

Thermal Quasi-Reflectography: A New Imaging Tool in Art Conservation. Claudia Daffara et al. in *Optics Express,* Vol. 20, No. 3, pages 14,746–14,753; June 18, 2012.

FROM OUR ARCHIVES

New Chemical Tools to Create Plastics. John A. Ewen; May 1997.

RECOMMENDED

By Clara Moskowitz

MORE TO EXPLORE
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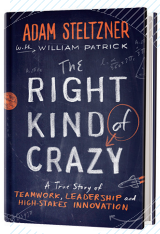
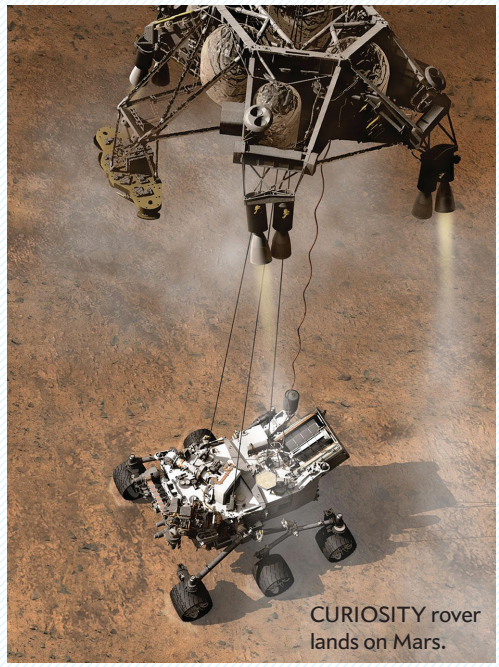
The Right Kind of Crazy: A True Story of Teamwork, Leadership, and High-Stakes Innovation

by Adam Steltzner, with William Patrick. Portfolio, 2016 ($28)



Less than a week before NASA's Curiosity rover was to land on Mars, an engineer on the team planning its touchdown found a problem: the three coordinates that determined the vehicle's "center of navigation" in its onboard computer were off. The team members faced a daunting decision: live with the minor error, which might have no effect on the landing, or update the coordinates and risk setting off other problems by making such a significant change so late in the game. They decided to alter the numbers—apparently a good call, because the rover famously made a flawless descent using its unprecedented "sky crane" landing system, which lowered the rover on cables from a spacecraft hanging above.

Steltzner, leader of Curiosity's entry, descent and landing team, with writer Patrick, recounts the challenges and thrills of planning the most complex planetary landing mechanism ever designed—a system he helped convince NASA's chief was "the right kind of crazy."



CURIOSITY rover lands on Mars.

NASA/JPL-CALTECH

Snowball in a Blizzard: A Physician's Notes on Uncertainty in Medicine

by Steven Hatch. Basic Books, 2016 ($27.99)

Uncertainty lies at the heart of modern medicine in ways that most physicians—not to mention their patients—often fail to recognize. Fundamental imperfections in our understanding of health and disease limit doctors' ability to combat illness. Hatch, an assistant professor of medicine at the University of Massachusetts Medical School, argues that physicians who ignore this uncertainty often overtreat their patients, resulting in sometimes harmful, even fatal consequences.

By the same token, far too many patients assume that more medical care is always better than less, thereby seeking or consenting to toxic treatments that trigger needless suffering. Hatch provides examples from such fields as breast cancer, cardiology and infectious disease. He also offers straightforward rules of thumb to help readers navigate medical advice. —*Christine Gorman*

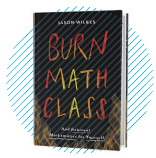
The Genius of Birds

by Jennifer Ackerman. Penguin Press, 2016 ($28)

Science journalist Ackerman sets out to show that being called a "birdbrain" should be a compliment, not an insult. Birds' clever social and environmental problem-solving skills, she shows, establish them among the most intelligent members of the animal kingdom. Crows frequently steal the show: for example, they craft tools, such as branching twigs perfectly pruned into solitary sticks that can retrieve meat from plastic tubes. Even birdsong is cause for admiration: some birds' ability to hear a sound and re-create it has much in common with our own capacity to learn language.

Ackerman devotes each chapter to a different bird skill and ends the book with a discussion of avian adaptive capabilities, which will prove vital in the near future as climate change and loss of habitat have put more than half of North American bird species at risk, according to the Audubon Society.

—*Jennifer Hackett*



Burn Math Class: And Reinvent Mathematics for Yourself

by Jason Wilkes. Basic Books, 2016 ($29.99)

Uninspired and unnecessarily complicated math courses have hidden the beauty of the discipline from many of us, asserts Wilkes, who has a background in mathematics. The cheekily named *Burn Math Class* is an informal primer on basic mathematical concepts meant to help people rediscover this beauty. He reinvigorates standard high school math topics through creative explanations and illuminating examples. For instance, he banishes the FOIL mnemonic ("first, outer, inner, last") often taught to students for solving $(a + b)^2$ and replaces it with a method that turns the equation into the area of a square, making the problem easy to solve without memorization.

Although Wilkes aims to reach the mathematically disinclined, math fans should be intrigued by his informal approach and determination to give the field a popularity boost. —*J.H.*

Michael Shermer is publisher of *Skeptic* magazine (www.skeptic.com). His book *The Moral Arc* (Henry Holt, 2015) is now out in paperback. Follow him on Twitter @michaelshermer

Hooey. Drivel. Baloney …

Would you know it if you saw it?

By Michael Shermer

Babble, bafflegab, balderdash, bilge, blabber, blarney, blather, bollocks, bosh, bunkum. These are a few of the synonyms (from just the b's) for the demotic descriptor BS (as commonly abbreviated). The *Oxford English Dictionary* equates it with "nonsense." In his best-selling 2005 book on the subject, Princeton University philosopher Harry Frankfurt famously distinguished BS from lying: "It is impossible for someone to lie unless he thinks he knows the truth. Producing bullshit requires no such conviction." BS may or may not be true, but its "truthiness" (in comedian Stephen Colbert's famous neologism) is meant to impress through obfuscation—that is, by saying something that sounds profound but may be nonsense.

Example: "Attention and intention are the mechanics of manifestation." This is an actual tweet composed by Deepak Chopra, as quoted by University of Waterloo psychologist Gordon Pennycook and his colleagues in a paper published in the November 2015 issue of *Judgment and Decision Making*. The scientists set out to determine "the factors that predispose one to become or to resist becoming" a victim of what they called "pseudo-profound" BS, or language "constructed to impress upon the reader some sense of profundity at the expense of a clear exposition of meaning or truth." I was cited in the paper for describing Chopra's language as "woo-woo nonsense." For instance, in a 2010 debate we had at the California Institute of Technology that was televised on ABC's *Nightline,* in the audience Q&A (http://bit.ly/1PQqk6s), Chopra defines consciousness as "a superposition of possibilities," to which physicist Leonard Mlodinow replies: "I know what each of those words mean. I still don't think I know.…"

Chopra's definition of consciousness certainly sounds like pseudo-profundity, but I have since gotten to know him and can assure readers that he doesn't create such phrases to intentionally obscure meaning. He believes that quantum physics explains consciousness, so invoking terms from that field makes sense in his mind, even though to those not so inclined, much of what he says sounds like, well, BS.

These are examples of what cognitive psychologist Dan Sperber meant when he wrote in "The Guru Effect," a 2010 article in the *Review of Philosophy and Psychology:* "All too often, what readers do is judge profound what they have failed to grasp." To find out if some people are more or less inclined to accept BS as legit based on their ability (or lack thereof) to grasp language (or lack thereof), Pennycook et al. began by distinguishing two types of thinking: one, intuitive—rapid and automatic cognition—and, two, reflective—slower and effortful cognition. Type 1 thinking makes us vulnerable to BS because it takes time and effort to think (and say), "I know what each of those words mean. I still don't think I know.…" Pennycook and his team tested the hypothesis that higher intelligence and a superior analytical cognitive style (analyticity) leads to a greater capacity to detect and reject pretentious BS. Employing standard measures of intelligence (for example, the Wordsum test) and analyticity (for example, the Cognitive Reflection Test), the psychologists presented subjects with a number of meaningless statements produced by the New Age Bullshit Generator (http://sebpearce.com/bullshit), such as "We are in the midst of a self-aware blossoming of being that will align us with the nexus itself" and "Today, science tells us that the essence of nature is joy."

In four studies on more than 800 subjects, the authors found that the higher the intelligence and analyticity of subjects, the less likely they were to rate such statements as profound. Conversely, and revealingly, they concluded that those most receptive to pseudo-profound BS are also more prone to "conspiratorial ideation, are more likely to hold religious and paranormal beliefs, and are more likely to endorse complementary and alternative medicine." Apropos of one of this column's skeptical leitmotifs, detecting BS, according to the authors, "is not merely a matter of indiscriminate skepticism but rather a discernment of deceptive vagueness in otherwise impressive sounding claims."

Skepticism should never be indiscriminate and should always be discerning of a claim's verisimilitude based on evidence and logic, regardless of language. But language matters, so it is incumbent on us all to transduce our neuro-phonemic excitatory action potentials into laconic phonological resonances unencumbered by extraneous and obfuscating utterances. And that's no BS. SA

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Illustration by Izhar Cohen

There Are No Words

English lacks some felicitous words it could really use

By Steve Mirsky

When I was in grade school, we were fed the now disputed notion that Eskimo languages, reflecting local concerns, had an unusually large number of words for snow. But nobody told us about the Inuit word *iktsuarpok,* which would have come in handy to describe one's behavior after putting in a call for a pizza delivery. *Iktsuarpok* "refers to the anticipation one feels when waiting for someone, whereby one keeps going outside to check if they have arrived." So writes University of East London psychologist Tim Lomas in a cross-cultural linguistics study for the *Journal of Positive Psychology.*

Lomas's paper is entitled "Towards a Positive Cross-Cultural Lexicography: Enriching Our Emotional Landscape through 216 'Untranslatable' Words Pertaining to Well-Being." The 216 words in question, the first cull of Lomas's mostly Web-based searches, can of course be at least loosely translated, which explains the qualifying quotation marks around untranslatable. Lomas explains that the words "are deemed 'untranslatable' to the extent that other languages lack a single word/phrase for the phenomenon." And let me tell you, his parents must be kvelling over his publication. The Yiddish word *kvell,* to use the many English words required in the paper, means "to glow with pride and happiness at the successes of others (often family members)." So much easier to simply kvell.

But can any mom and dad truly kvell without access to the word? Or is their emotional experience limited by the words available in their native language? "The existence of 'untranslatable' words pertaining to well-being implies that there are positive emotional states which have hitherto only been explicitly recognised by particular cultures," Lomas writes. "However, this does not mean that people in other cultures may not have had a comparable experience. Yet, lacking a specific term for it, such people have arguably not had the opportunity to specifically identify that particular state, which instead thus becomes just another un-conceptualised ripple in the on-going flux of subjective experience."

In other words, his parents could indeed probably kvell even if they don't speak Yiddish. (Whether they got all the *nachas* they had coming is another question.) "However," he writes, "the value of exploring 'untranslatable' words is that, if people are introduced to a foreign term, this may then be used to give voice to these hitherto unlabelled states."

So let's give voice, using some of Lomas's excavated non-English words, to some hitherto unlabeled states and possibly enrich our emotional landscape.

Ever keep eating even when full because to do so was just so damn enjoyable? The Georgian word *shemomedjamo* describes this phenomenon. It's also the sound that comes out of you a few hours later. Portuguese has *desbundar* to capture becoming uninhibited while having fun. Bantu's even more specific *mbukimvuki* involves whipping off your clothes to dance. Hey, it's tough to dance in tight pants.

One of life's great pleasures (memorably captured in the movie *The Shawshank Redemption*) is drinking beer outside on a hot day, which is *utepils* in Norwegian. Drink too much and thereby come up with an ingenious plan, and you've committed the German *Schnapsidee.* Try to realize that plan, and your enemies will no doubt be filled with *Schadenfreude,* an example of a word so good that English simply imported it. Yes, we English speakers are word *banditos.*

I had no idea until I read Lomas that I had many times engaged in *gökotta.* That's Swedish for waking up early to go outside to hear the morning's first birds sing. In the right setting, *gökotta* can help fulfill your *prostor.* That's the Russian word Lomas's paper cites as capturing "a desire for spaciousness, roaming free in limitless expanses, not only physically, but creatively and spiritually." You might concurrently achieve *Waldeinsamkeit,* German for the mysterious, and possibly slightly creepy, solitude available when alone in the woods.

Once your *Wanderlust* is quenched, you can contribute to Lomas's research. Just go to www.drtimlomas.com/lexicography to add any "untranslatable" words he has yet to uncover. It might even be good for your *karma.* SA

Steve Mirsky has been writing the Anti Gravity column since a typical tectonic plate was about 35 inches from its current location. He also hosts the *Scientific American* podcast Science Talk.

SCIENTIFIC AMERICAN ONLINE
COMMENT ON THIS ARTICLE AT
SCIENTIFICAMERICAN.COM/APR2016

Illustration by Matt Collins

April 1966

Technology and Employment

"According to the National Commission on Technology, Automation, and Economic Progress, the 'vast majority' of people recognize that technological change 'has led to better working conditions by eliminating many, perhaps most, dirty, menial and servile jobs.… Perhaps the [concern] most responsible for the establishment of the Commission has arisen from the belief that technological change is a major source of unemployment…, that eventually it would eliminate all but a few jobs.' The members of the commission, for their part, concluded 'that technology eliminates jobs, not work.'"

X-ray Cosmology

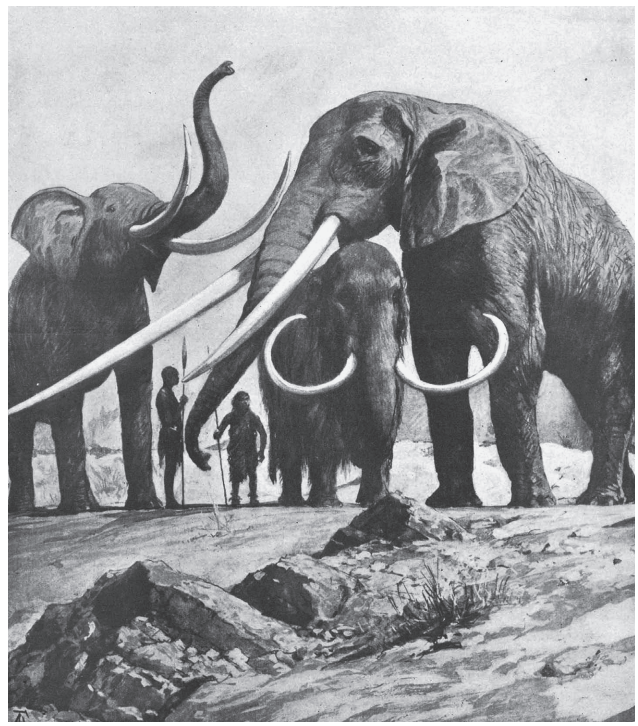
"The first two sources of X radiation outside our galaxy have been discovered in data obtained a year ago by means of rocket-borne X-ray detectors. The new sources have been identified by their discoverers at the U.S. Naval Research Laboratory as coinciding with two of the most powerful radio-emitting galaxies, designated Cygnus A and M 87. The X radiation from both galaxies appears to be from 10 to 100 times stronger than the energy they emit in the form of light and radio waves. Because the earth's atmosphere is essentially opaque to X rays from space, instruments are placed above most of the atmosphere by means of Aerobee rockets fired from the White Sands Proving Ground in New Mexico."

men been so vast as at present, when the European war has added tens of thousands to the already large number of such unfortunates. Recently, however, the French have also endeavored to create various diversions for those whom the war has deprived of their sight, among which is fencing. To the lay mind it is indeed difficult to conceive how an active sport such as fencing can be indulged in by sightless persons. Yet fencing tournaments in which blind men are the only participants are now common in Paris."

The Largest Elephant

"Three or four years ago a party of Royal Engineers were digging a trench on the banks of the Medway, at Upnor, opposite Chatham Dockyard. They came across a number of bones and part of a huge tusk. Not until the summer of 1915, however, was it found possible to accomplish the task of salvaging these remains. The limb-bones of the straight-tusked elephant (*Elephas antiquus*) afford very convincing evidence as to the size of this animal, which must have been enormous. It is calculated, indeed, that it must have stood at least 15 feet high [*see illustration*], which far exceeds that of any other species living or extinct."

Images from the science of natural history in 1916 are at www.ScientificAmerican.com/apr2016/natural-history

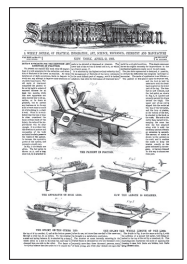


1916: Gigantic straight-tusked *Elephas antiquus* hobnobs with a mammoth and an African elephant in this artist's conception.

April 1916

Sports for the Blind

"Never before has the problem of finding employment for blind



April 1866

Paper from Wood

"The Manayunk Pulp Works, we were informed, were completed during the present month. These are without doubt the most extensive works of the kind in the world, and are capable of producing from twelve to fifteen tons of paper pulp per diem. These works will increase the daily production of printing paper by about 13,000 pounds, lessening to that extent the consumption of rags, thus diminishing the price of both. The present process for pulping wood was begun about the year 1850, by Mr. Hugh Burgess."

The "soda process," co-invented by Burgess, efficiently extracted cellulose from wood.

High-Tech Goofing Off

"The diving bell has been abandoned on the Thames in favor of the diving bell dress [diving suit], because the men employed were found, while the Westminster Bridge was being built, to spend their time at the bottom in playing cards, and there was of course no effectual means of keeping a check on them. It is not easy to play cards in a diving dress alone, however, and the remedy has proved very satisfactory in its operations."

SCIENTIFIC AMERICAN SUPPLEMENT, VOL. LXXXI, NO. 2101, APRIL 8, 1916

SCIENTIFIC AMERICAN ONLINE
FOR MORE ON ZIKA IN THE U.S., GO TO
SCIENTIFICAMERICAN.COM/APR2016/GRAPHIC-SCIENCE

Travels with Zika

The mosquito-borne virus migrates to the U.S. from diverse nations

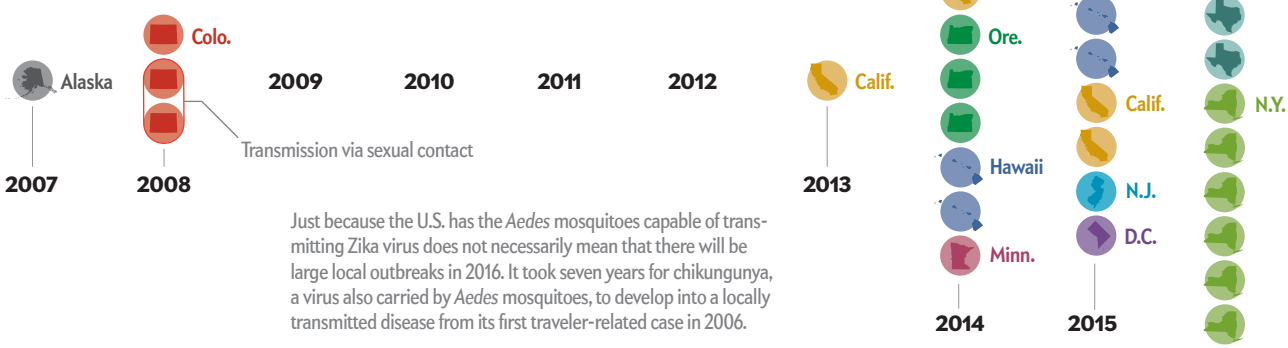
Zika burst into the international news this year, along with travel alerts, heartbreaking images of children with birth defects and a link to an autoimmune disease that can cause paralysis. The virus first surfaced in this country back in 2007, when an American medical volunteer contracted the disease during an outbreak in Micronesia and then became sick with it back in Alaska. Since then, more than 50 cases have been identified in the U.S. Almost every one of these patients contracted Zika while abroad, but at least two infections were acquired via sexual contact.

Because the U.S. Centers for Disease Control and Prevention does not provide detailed state-by-state breakdowns of Zika cases, Scientific American gathered and analyzed information from the health departments of all 50 states and the District of Columbia and followed up with some county and city health officials. The result is this exclusive map of how the virus first made its way to the U.S.

—Dina Fine Maron

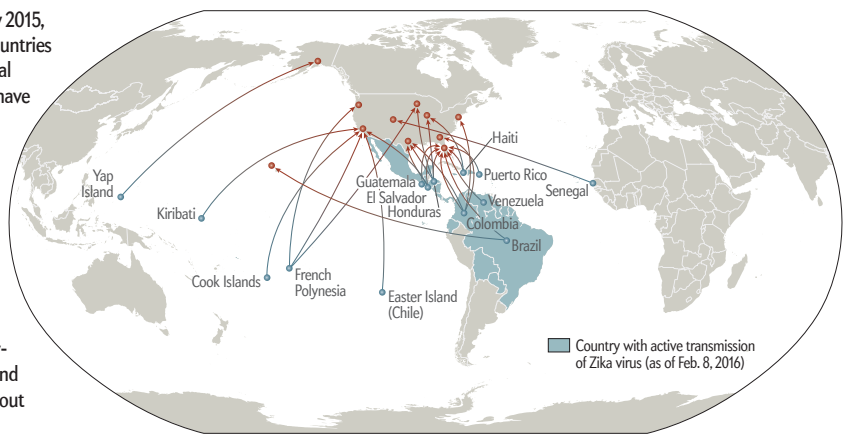
The only instance of local Zika virus transmission from sexual contact during the current outbreak occurred in Texas. State and federal health officials, however, are bracing themselves for future clusters of disease in the U.S. transmitted by mosquitoes living in the country.

Number of Zika cases reported in the U.S. as of February 8, 2016



Just because the U.S. has the *Aedes* mosquitoes capable of transmitting Zika virus does not necessarily mean that there will be large local outbreaks in 2016. It took seven years for chikungunya, a virus also carried by *Aedes* mosquitoes, to develop into a locally transmitted disease from its first traveler-related case in 2006.

Since Zika was detected in Brazil in May 2015, the virus has spread to more than 30 countries and territories globally (mostly in Central and South America), and U.S. travelers have brought the virus back from more than a dozen of them. Before 2007, at least 14 cases of Zika virus were documented in the entire world, but others most likely never made it into the literature. The World Health Organization (WHO) expects between three million and four million cases in 2016, although most will be asymptomatic. The WHO says that Zika could now show up everywhere in the Americas except Canada and continental Chile—the only places without the vector mosquitoes.



SOURCE: U.S. CENTERS FOR DISEASE CONTROL AND PREVENTION (*countries with active transmission*)

Map by Mapping Specialists, Graphic by Jen Christiansen